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STAFF REPORT to the NIDA DIRECTOR

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RESEARCH FINDINGS

BASIC NEUROSCIENCE AND BEHAVIORAL RESEARCH

A Novel Model Of Chronic Sleep Restriction Reveals An Increase In the Perceived Incentive Reward Value Of Cocaine In High Drug-Taking Rats. Puhl MD, Boisvert M, Guan Z, Fang J, Grigson PS. Pharmacol Biochem Behav. 2013; 109: 8-15.

Substance abuse and sleep deprivation are major problems in our society. Clinical studies suggest that measures of poor sleep quality effectively predict relapse to substance abuse. Previously, the authors' laboratory has shown that acute sleep deprivation increases the rate and efficiency (i.e., the goal-directed nature of responding) of cocaine self-administration using a progressive ratio (PR) schedule of reinforcement. However, the problem of sleep deprivation in our nation is largely one of chronicity. Therefore, the current study used a rodent model of chronic sleep restriction more akin to that experienced by humans (approximately 25% reduction in baseline sleep over the course of 8 days) to assess the impact of chronic sleep deprivation on cocaine-seeking and cocaine-taking behaviors in rats early during acquisition of self-administration. While low drug-taking rats were unaffected by chronic sleep restriction, high drug-takers in the chronic sleep restriction (CSR) group exhibited enhanced fixed ratio (FR) responding by the fourth day of FR training and significantly higher PR breakpoints than their non-sleep restriction (NSR) counterparts. This study is the first to directly assess the impact of chronic sleep deprivation on drug self-administration. These results show that chronic sleep deprivation early during acquisition of self-administration has a significant effect on the perceived incentive reward value of cocaine in high drug-takers, as indicated by both increased FR responding and an increased willingness to work for drug. Thus, it is important to be mindful of such factors in clinical settings designed for treatment of addiction and relapse prevention.

Optogenetic Evidence That Pallidal Projections, Not Nigral Projections, From the Nucleus Accumbens Core Are Necessary For Reinstating Cocaine Seeking. Stefanik MT, Kupchik YM, Brown RM, Kalivas PW. J Neurosci 2013; 33: 13654-13662.

The core subcompartment of the nucleus accumbens (NAcore) contributes significantly to behavioral responses following motivationally relevant stimuli, including drug-induced, stress-induced, and cue-induced reinstatement of cocaine seeking. Projections from NAcore that could carry information necessary to initiate reinstated cocaine seeking include outputs via the indirect pathway to the dorsolateral subcompartment of the ventral pallidum (dlVP) and through the direct pathway to the medial substantia nigra (SN). Here the authors used an optogenetic strategy to determine whether the dlVP or nigral projections from the NAcore are necessary for cocaine seeking initiated by a cocaine and conditioned cue combination in rats extinguished from cocaine self-administration. Rats were pretreated in the NAcore with an adeno-associated virus expressing the inhibitory opsin archaerhodopsin, and fiber-optic cannulae were implanted above the indirect pathway axon terminal field in the dlVP, or the direct pathway terminal field in the SN. Inhibiting the indirect pathway to the dlVP, but not the direct pathway to the SN, prevented cocaine-plus-cue-induced reinstatement. The authors also examined projections back to the NAcore from the ventral tegmental area (VTA) and dlVP. Inhibiting the dlVP to NAcore projection did not alter, while inhibiting VTA afferents abolished reinstated cocaine seeking. Localization of green fluorescent protein reporter expression and whole-cell patch electrophysiology were used to verify opsin expression. These data reveal a circuit involving activation of VTA inputs to the NAcore and

NAcore projections through the indirect pathway to the dlVP as critical for cocaine-plus-cue-induced reinstatement of cocaine seeking.

An Intronic Variant In OPRD1 Predicts Treatment Outcome For Opioid Dependence In African-Americans. Crist RC, Clarke TK, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. Neuropsychopharmacology. 2013; 38(10): 2003-2010.
Although buprenorphine and methadone are both effective treatments for opioid dependence, their efficacy can vary significantly among patients. Genetic differences may explain some of the variability in treatment outcome. Understanding the interactions between genetic background and pharmacotherapy may result in more informed treatment decisions. This study is a pharmacogenetic analysis of the effects of genetic variants in OPRD1, the gene encoding the δ-opioid receptor, on the prevalence of opioid-positive urine tests in African-Americans (n=77) or European-Americans (n=566) undergoing treatment for opioid dependence. Patients were randomly assigned to treatment with either methadone or buprenorphine/naloxone (Suboxone) over a 24-week open-label clinical trial, in which illicit opioid use was measured by weekly urinalysis. In African-Americans, the intronic SNP rs678849 predicted treatment outcome for both medications. Methadone patients with the CC genotype were less likely to have opioid-positive urine tests than those in the combined CT and TT genotypes group (relative risk (RR)=0.52, 95% confidence interval (CI)=0.44-0.60, p=0.001). In the buprenorphine treatment group, however, individuals with the CC genotype were more likely to have positive opioid drug screens than individuals in the combined CT and TT genotypes group (RR=2.17, 95% CI=1.95-2.68, p=0.008). These findings indicate that the genotype at rs678849 predicts African-American patient response to two common treatments for opioid dependence, suggesting that matching patients to treatment type based on the genotype at this locus may improve overall treatment efficacy. This observation requires confirmation in an independent population.

C57BL/6N Mutation In Cytoplasmic FMRP Interacting Protein 2 Regulates Cocaine Response. Kumar V, Kim K, Joseph C, Kourrich S, Yoo SH, Huang HC, Vitaterna MH, de Villena FP, Churchill G, Bonci A, Takahashi JS. Science. 2013 Dec 20; 342(6165): 1508-1512
The inbred mouse C57BL/6J is the reference strain for genome sequence and for most behavioral and physiological phenotypes. However, the International Knockout Mouse Consortium uses an embryonic stem cell line derived from a related C57BL/6N substrain. The authors found that C57BL/6N has a lower acute and sensitized response to cocaine and methamphetamine. They mapped a single causative locus and identified a nonsynonymous mutation of serine to phenylalanine (S968F) in Cytoplasmic FMRP interacting protein 2 (Cyfip2) as the causative variant. The S968F mutation destabilizes CYFIP2, and deletion of the C57BL/6N mutant allele leads to acute and sensitized cocaine-response phenotypes. The authors propose that CYFIP2 is a key regulator of cocaine response in mammals and present a framework to use mouse substrains to identify previously unknown genes and alleles regulating behavior.

Methamphetamine Inhibits Toll-Like Receptor 9-Mediated Anti-HIV Activity In Macrophages. Cen P, Ye L, Su QJ, Wang X, Li JL, Lin XQ, Liang H, Ho WZ. AIDS Res Hum Retroviruses. 2013; 29(8): 1129-1137.
Toll-like receptor 9 (TLR9) is one of the key sensors that recognize viral infection/replication in the host cells. Studies have demonstrated that methamphetamine (METH) dysregulated host cell innate immunity and facilitated HIV infection of macrophages. In this study, the authors present new evidence that METH suppressed TLR9-mediated anti-HIV activity in macrophages. Activation of

TLR9 by its agonist CpG-ODN 2216 inhibits HIV replication, which was demonstrated by increased expression of TLR9, interferon (IFN)-α, IFN regulatory factor-7 (IRF-7), myeloid differentiation factor 88 (MyD88), and myxovirus resistance gene A (MxA) in macrophages. However, METH treatment of macrophages greatly compromised the TLR9 signaling-mediated anti-HIV effect and inhibited the expression of TLR9 downstream signaling factors. Dopamine D1 receptor (D1R) antagonists (SCH23390) could block METH-mediated inhibition of anti-HIV activity of TLR9 signaling. Investigation of the underlying mechanisms of the METH action showed that METH treatment selectively down-regulated the expression of TLR9 on macrophages, whereas it had little effect on the expression of other TLRs. Collectively, our results provide further evidence that METH suppresses host cell innate immunity against HIV infection by down-regulating TLR9 expression and its signaling-mediated antiviral effect in macrophages.

Outcome Specificity In Deepened Extinction May Limit Treatment Feasibility: Co-Presentation Of A Food Cue Interferes With Extinction Of Cue-Elicited Cocaine Seeking.
Tunstall BJ, Verendeev A, Kearns DN. Drug Alcohol Depend. 2013; 133(3): 832-837.
The authors previously showed that presenting two cocaine cues simultaneously during extinction deepens the extinction of cue-elicited cocaine seeking (Kearns et al., 2012). The present study investigated whether compounding a non-drug appetitive cue with a cocaine cue would similarly deepen extinction. In Experiment 1, tone and click were each first established as discriminative stimuli for cocaine-reinforced responding and light was a cue for food-reinforced responding. In an initial extinction phase, all stimuli were presented individually. Then, during an additional compound extinction session, rats received 8 presentations of one of the cocaine cues (counterbalanced over subjects) simultaneously with light and 8 presentations of the other cue alone. A spontaneous recovery test was used to evaluate the effectiveness of the extinction treatments. Experiment 2 was performed under conditions designed to match those of Experiment 1, except food was the reinforcer in tone and click instead of cocaine. In Experiment 1, the cocaine cue compounded with the food cue during extinction controlled greater spontaneous recovery of cocaine seeking than the cocaine cue always presented alone. In contrast, Experiment 2 demonstrated deepened extinction of responding to a food cue when both compounded cues were food cues. Results suggest that deepened extinction depends on the compound presentation of cues associated with the same reinforcer. Compound presentation of cues associated with different reinforcers could lead to an enhancement of responding. Care is urged in attempts to deepen the extinction of cue-elicited drug seeking by compounding drug cues with non-drug cues.

Intravenous Prenatal Nicotine Exposure Increases Orexin Expression In the Lateral Hypothalamus And Orexin Innervation Of the Ventral Tegmental Area In Adult Male Rats.
Morgan AJ, Harrod SB, Lacy RT, Stanley EM, Fadel JR. Drug Alcohol Depend. 2013; 132(3): 562-570.
Approximately 18% of pregnant women continue to smoke tobacco cigarettes throughout pregnancy. Offspring exposed to tobacco smoke in utero exhibit a higher incidence of drug use in later stages of development relative to non-exposed children. Animal models indicate that prenatal nicotine (PN) exposure alone alters the development of the mesocorticolimbic dopamine (DA) system, which, in part, organizes motivated behavior and reward. The orexin/hypocretin neuropeptide system, which originates in the lateral hypothalamus (LH), projects to key areas of the mesocorticolimbic DA pathway. Previous research suggests that orexin exerts a major influence on motivation and reward. The present experiments determined if intravenous (IV) PN exposure alters (1) the expression of orexin neurons and melanin-concentrating hormone (MCH; positive control) in the LH; and (2) orexin projections from the LH onto DA neurons in the ventral tegmental area

(VTA). Dams were injected with IV nicotine (0.05 mg/kg/injection) or saline 3×/day during gestational days 8-21. Tissues from adult male offspring (~130 days) were examined using immunohistochemistry. Relative to controls, offspring of IV PN exposure showed (1) increased numbers of orexin neurons in the LH, and no changes in the expression of MCH; and (2) increased orexin appositions on DA cells in the VTA. The findings indicate that the influence of PN exposure is enduring, and suggests that the PN-induced modification of orexin expression on mesolimbic circuitry may contribute to the reported changes in motivated behaviors related to food and drug reward observed in offspring prenatally exposed to nicotine.

The Novel Recreational Drug 3,4-Methylenedioxypyrovalerone (MDPV) Is A Potent Psychomotor Stimulant: Self-Administration and Locomotor Activity In Rats. Aarde SM, Huang PK, Creehan KM, Dickerson TJ, Taffe MA. Neuropharmacology 2013; 71: 130-140. Recreational use of the cathinone derivative 3,4-methylenedioxypyrovalerone (MDPV; "bath salts") has increased worldwide in past years, accompanied by accounts of health and legal problems in the popular media and efforts to criminalize possession in numerous jurisdictions. Minimal information exists on the effects of MDPV in laboratory models. This study determined the effects of MDPV, alongside those of the better studied stimulant d-methamphetamine (METH), using rodent models of intravenous self-administration (IVSA), thermoregulation and locomotor activity. Male Wistar rats were trained to self-administer MDPV or METH (0.05 mg/kg/infusion, i.v.) or were prepared with radiotelemetry implants for the assessment of body temperature and activity responses to MDPV or METH (0-5.6 mg/kg s.c.). METH and MDPV were consistently self-administered within 10 training sessions (mg/kg/h; METH Mean = 0.4 and Max = 1.15; MDPV Mean = 0.9 and Max = 5.8). Dose-substitution studies demonstrated that behavior was sensitive to dose for both drugs, but MDPV (0.01-0.50 mg/kg/inf) showed greater potency and efficacy than METH (0.1-0.25 mg/kg/inf). In addition, both MDPV and METH increased locomotor activity at lower doses (0.5-1.0 mg/kg, s.c.) and transiently decreased activity at the highest dose (5.6 mg/kg, s.c.). Body temperature increased monotonically with increasing doses of METH but MDPV had a negligible effect on temperature. Stereotypy was associated with relatively high self-administered cumulative doses of MDPV (~1.5 mg/kg/h) as well as with non-contingent MDPV administration wherein the intensity and duration of stereotypy increased as MDPV dose increased. Thus, MDPV poses a substantial threat for compulsive use that is potentially greater than that for METH.

Deep Brain Stimulation Of the Nucleus Accumbens Shell Attenuates Cocaine Reinstatement Through Local and Antidromic Activation. Vassoler FM, White SL, Hopkins TJ, Guercio LA, Espallergues J, Berton O, Schmidt HD, Pierce RC. J Neurosci. 2013; 33(36): 14446-14454. Accumbal deep brain stimulation (DBS) is a promising therapeutic modality for the treatment of addiction. Here, the authors demonstrate that DBS in the nucleus accumbens shell, but not the core, attenuates cocaine priming-induced reinstatement of drug seeking, an animal model of relapse, in male Sprague Dawley rats. Next, they compared DBS of the shell with pharmacological inactivation. Results indicated that inactivation using reagents that influenced (lidocaine) or spared (GABA receptor agonists) fibers of passage blocked cocaine reinstatement when administered into the core but not the shell. It seems unlikely, therefore, that intrashell DBS influences cocaine reinstatement by inactivating this nucleus or the fibers coursing through it. To examine potential circuit-wide changes, c-Fos immunohistochemistry was used to examine neuronal activation following DBS of the nucleus accumbens shell. Intrashell DBS increased c-Fos induction at the site of stimulation as well as in the infralimbic cortex, but had no effect on the dorsal striatum, prelimbic cortex, or ventral pallidum. Recent evidence indicates that accumbens DBS antidromically stimulates axon terminals, which ultimately activates GABAergic interneurons in cortical areas that

send afferents to the shell. To test this hypothesis, GABA receptor agonists (baclofen/muscimol) were microinjected into the anterior cingulate, and prelimbic or infralimbic cortices before cocaine reinstatement. Pharmacological inactivation of all three medial prefrontal cortical subregions attenuated the reinstatement of cocaine seeking. These results are consistent with DBS of the accumbens shell attenuating cocaine reinstatement via local activation and/or activation of GABAergic interneurons in the medial prefrontal cortex via antidromic stimulation of cortico-accumbal afferents.

Temporal Pattern Of Cocaine Intake Determines Tolerance Vs Sensitization Of Cocaine Effects At the Dopamine Transporter. Calipari ES, Ferris MJ, Zimmer BA, Roberts DCS, Jones SR. Neuropsychopharmacology 2013; 38(12): 2385-2392.

The dopamine transporter (DAT) is responsible for terminating dopamine (DA) signaling and is the primary site of cocaine's reinforcing actions. Cocaine self-administration has been shown previously to result in changes in cocaine potency at the DAT. To determine whether the DAT changes associated with self-administration are due to differences in intake levels or temporal patterns of cocaine-induced DAT inhibition, the authors manipulated cocaine access to produce either continuous or intermittent elevations in cocaine brain levels. Long-access (LgA, 6h) and short-access (ShA, 2h) continuous self-administration produced similar temporal profiles of cocaine intake that were sustained throughout the session; however, LgA had greater intake. ShA and intermittent-access (IntA, 6h) produced the same intake, but different temporal profiles, with 'spiking' brain levels in IntA compared with constant levels in ShA. IntA consisted of 5-min access periods alternating with 25-min timeouts, which resulted in bursts of high responding followed by periods of no responding. DA release and uptake, as well as the potency of cocaine for DAT inhibition, were assessed by voltammetry in the nucleus accumbens slices following control, IntA, ShA, and LgA self-administration. Continuous-access protocols (LgA and ShA) did not change DA parameters, but the 'spiking' protocol (IntA) increased both release and uptake of DA. In addition, high continuous intake (LgA) produced tolerance to cocaine, while 'spiking' (IntA) produced sensitization, relative to ShA and naïve controls. Thus, intake and pattern can both influence cocaine potency, and tolerance seems to be produced by high intake, while sensitization is produced by intermittent temporal patterns of intake.

Cocaine Self-Administration Abolishes Associative Neural Encoding in the Nucleus Accumbens Necessary for Higher-Order Learning. Saddoris MP, Carelli RM. Biol Psychiatry 2013. Epub ahead of print.

Cocaine use is often associated with diminished cognitive function, persisting even after abstinence from the drug. Likely targets for these changes are the core and shell of the nucleus accumbens (NAc), which are critical for mediating the rewarding aspects of drugs of abuse as well as supporting associative learning. To understand this deficit, the authors recorded neural activity in the NAc of rats with a history of cocaine self-administration or control subjects while they learned Pavlovian first- and second-order associations. Rats were trained for 2 weeks to self-administer intravenous cocaine or water. Later, rats learned a first-order Pavlovian discrimination where a conditioned stimulus (CS)+ predicted food, and a control (CS-) did not. Rats then learned a second-order association where, absent any food reinforcement, a novel cued (SOC+) predicted the CS+ and another (SOC-) predicted the CS-. Electrophysiological recordings were taken during performance of these tasks in the NAc core and shell. Both control subjects and cocaine-experienced rats learned the first-order association, but only control subjects learned the second-order association. Neural recordings indicated that core and shell neurons encoded task-relevant information that correlated with behavioral performance, whereas this type of encoding was

abolished in cocaine-experienced rats. The NAc core and shell perform complementary roles in supporting normal associative learning, functions that are impaired after cocaine experience. This impoverished encoding of motivational behavior, even after abstinence from the drug, might provide a key mechanism to understand why addiction remains a chronically relapsing disorder despite repeated attempts at sobriety.

Diminished Role of Dopamine D1-Receptor Signaling with the Development of an Addicted Phenotype in Rats. Ramoa CP, Doyle SE, Lycas MD, Chernau AK, Lynch WJ. Biol Psychiatry 2013. Epub ahead of print.

Although considerable evidence implicates dopamine D1-receptor signaling in the nucleus accumbens in motivation for cocaine during early stages of addiction, less is known with regard to its role after the development of addiction. Here, the authors examined its role in the development of an addicted phenotype in intact male and female rats, and in female rats that were either resistant or vulnerable to developing this phenotype. Intact males, females, and ovariectomized (OVX) females with and without estradiol (vulnerable, OVX+E; resistant, OVX+Veh) were given either short access (ShA) (three fixed-ratio 1 sessions, maximum of 20 infusions) or 24-hour extended access (ExA) to cocaine for 10 days (4 trials/hour). Motivation for cocaine was assessed after a 14-day abstinence period with a progressive-ratio schedule. Once responding stabilized, the effects of intra-accumbens infusion of the D1-receptor antagonist, SCH-23390 (0, .3, 1.0, 3.0 μg), were examined. Motivation for cocaine was markedly higher after abstinence from ExA versus ShA self-administration in intact males and females, indicating the development of an addicted phenotype in these groups. Motivation for cocaine was also higher than ShA control subjects in OVX+E but not OVX+Veh females after ExA self-administration, confirming the categorization of these groups as vulnerable versus resistant. After ExA self-administration, intact males and females and OVX+E but not OVX+Veh females were less sensitive to the effects of D1-receptor antagonism as compared with their ShA counterparts. These results suggest that the role of D1-receptor signaling, although critical in "nonaddicted" stages, becomes diminished once addiction has developed.

The Role of the Neurokinin-1 Receptor in Stress-Induced Reinstatement of Alcohol and Cocaine Seeking. Schank JR, King CE, Sun H, Cheng K, Rice KC, Heilig M, Weinshenker D, Schroeder JP. Neuropsychopharmacology 2013. Epub ahead of print.

Neurokinin-1 receptors (NK1Rs) have been shown to mediate alcohol and opiate, but not cocaine reward in rodents. The authors recently reported that NK1R antagonism also blocks stress-induced reinstatement of alcohol seeking in rats, but it is presently unknown whether these antirelapse properties extend to other drug classes. Although some work has suggested that intracranial substance P (SP) infusion reinstates cocaine seeking following extinction, no studies have indicated a direct role for the NK1R in reinstatement of cocaine seeking. Here, the authors explored the effect of the NK1R antagonist L822429 on yohimbine-induced reinstatement of alcohol or cocaine seeking in Long–Evans rats. Consistent with their previous findings with footshock-induced reinstatement of alcohol seeking in Wistar rats, the authors found that L822429 attenuates yohimbine-induced reinstatement of alcohol seeking, but does not affect baseline alcohol self-administration. They observed a similar suppression of yohimbine-induced reinstatement of cocaine seeking by L822429, and found that Long–Evans rats exhibit greater sensitivity to NK1R antagonism than Wistar rats. Accordingly, Long–Evans rats exhibit differences in the expression of NK1Rs in some subcortical brain regions. Combined, these findings suggest that while NK1R antagonism differentially influences alcohol- and cocaine-related behavior, this receptor mediates stress-induced seeking of both drugs.

Nicotine Modulation Of Adolescent Dopamine Receptor Signaling and Hypothalamic Peptide Response. Mojica CY, Dao JM, Yuan M, Loughlin SE, Leslie FM. Neuropharmacology 2014; 77: 285-293.

Adolescence is a sensitive developmental period for limbic and dopamine systems that coincides with the typical age for onset of tobacco use. The authors have previously shown that a 4-day, low-dose nicotine (0.06 mg/kg) pretreatment enhances locomotor and penile response to the D2-like agonist, quinpirole (0.4 mg/kg), in adolescent but not adult rats. The present study is designed to determine mechanisms underlying this effect. Nicotine enhancement of adolescent quinpirole-induced locomotion was mediated by D2 receptors (D2Rs) since it was blocked by the D2R antagonist, L-741,626, but not by the D3R and D4R antagonists, NGB 2904 and L-745,870. Enhancement of quinpirole-induced erectile response was blocked by both L-741,626 and NGB 2904, indicating involvement of D3Rs. Whereas D2R binding was unaffected by adolescent nicotine pretreatment, effector coupling in the striatum was increased, as determined by GTPγS binding. Nicotine pretreatment enhanced quinpirole-induced c-fos mRNA expression in the hypothalamic paraventricular and supraoptic nuclei in adolescents only. Adolescent nicotine pretreatment enhanced c-fos mRNA expression in corticotropin releasing factor (CRF) cells of the paraventricular nucleus, and enhancement of penile erection was blocked by the CRF-1 receptor antagonist, CP 376,396. These findings suggest that adolescent dopamine and CRF systems are vulnerable to alteration by nicotine. This is the first evidence for a role of CRF in adolescent erectile response.

Different Adaptations In AMPA Receptor Transmission In The Nucleus Accumbens After Short Vs Long Access Cocaine Self-Administration Regimens. Purgianto A, Scheyer AF, Loweth JA, Ford KA, Tseng KY, Wolf ME. Neuropsychopharmacology 2013; 38: 1789-1797.

Ca(2+)-permeable AMPA receptors (CP-AMPARs) accumulate in the nucleus accumbens (NAc) after ~1 month of withdrawal from a long-access cocaine self-administration regimen (6 h/d, 10d). This is functionally significant because CP-AMPARs mediate the 'incubated' cue-induced cocaine craving produced by this regimen. The authors' present goal was to determine if other commonly employed cocaine self-administration regimens also elicit CP-AMPAR accumulation. They compared four regimens, named according to whether sessions were short-access (ShA, 2 h) or long-access (LgA, 6 h) and the total number of sessions: LgA/10d (already shown to elicit CP-AMPAR accumulation), ShA/11d, ShA/20-24d, and LgA/20-24d. In the latter regimens, rats began with 10 days of ShA and then entered a differential phase (10-14 days) in which ShA sessions either continued or switched to LgA. Controls self-administered saline. After >40 days of withdrawal, whole-cell patch-clamp recordings were performed in NAc core medium spiny neurons to assess the contribution of CP-AMPAR transmission, based on the magnitude of synaptic suppression elicited by bath application of the selective CP-AMPAR antagonist naspm (100μM). Naspm produced a non-significant (~10%) attenuation of electrically evoked local excitatory postsynaptic current in the saline and ShA groups. By contrast, a significant naspm-induced synaptic attenuation (25-30%) was observed in both the LgA groups. Further analyses indicate that this emergence of CP-AMPAR transmission in the LgA groups is associated with increased baseline responsiveness of MSN to excitatory drive. Together with data on cocaine infusions in each group, these results show that CP-AMPAR accumulation and enhanced glutamate transmission is associated with longer sessions (6 h), rather than the number of sessions or cocaine infusions.

Ammonia Mediates Methamphetamine-Induced Increases in Glutamate and Excitotoxicity. Halpin LE, Northrop NA, Yamamoto BK. Neuropsychopharmacology. 2013. Epub ahead of print.
Ammonia has been identified to have a significant role in the long-term damage to dopamine and serotonin terminals produced by methamphetamine (METH), but how ammonia contributes to this damage is unknown. Experiments were conducted to identify whether increases in brain ammonia affect METH-induced increases in glutamate and subsequent excitotoxicity. Increases in striatal glutamate were measured using in vivo microdialysis. To examine the role of ammonia in mediating changes in extracellular glutamate after METH exposure, lactulose was used to decrease plasma and brain ammonia. Lactulose is a non-absorbable disaccharide, which alters the intestinal lumen through multiple mechanisms that lead to the increased peripheral excretion of ammonia. METH caused a significant increase in extracellular glutamate that was prevented by lactulose. Lactulose had no effect on METH-induced hyperthermia. To determine if ammonia contributed to excitotoxicity, the effect of METH and lactulose treatment on calpain-mediated spectrin proteolysis was measured. METH significantly increased calpain-specific spectrin breakdown products, and this increase was prevented with lactulose treatment. To examine if ammonia-induced increases in extracellular glutamate were mediated by excitatory amino-acid transporters, the reverse dialysis of ammonia, the glutamate transporter inhibitor, DL-threo-*-benzyloxyaspartic acid (TBOA), or the combination of the two directly into the striatum of awake, freely moving rats was conducted. TBOA blocked the increases in extracellular glutamate produced by the reverse dialysis of ammonia. These findings demonstrate that ammonia mediates METH-induced increases in extracellular glutamate through an excitatory amino-acid transporter to cause excitotoxicity.

Cocaine-Induced Adaptations In D1 and D2 Accumbens Projection Neurons (A Dichotomy Not Necessarily Synonymous With Direct and Indirect Pathways). Smith RJ, Lobo MK, Spencer S, Kalivas PW. Curr Opin Neurobiol 2013; 23: 546-552.
Cocaine exposure causes enduring neuroadaptations in ventral striatum, or nucleus accumbens (NAc), an area critically involved in reward learning and relapse of drug seeking. Medium spiny neurons (MSNs) in striatum are dichotomous in their expression of either D1 or D2 dopamine receptors, along with other receptors and neuropeptides. In dorsal striatum, these two subpopulations show non-overlapping innervation of distinct terminal fields via the direct or indirect pathways. However, NAc D1-MSNs and D2-MSNs are not fully segregated in this manner, with both cell types innervating ventral pallidum. Recent studies show that D1-MSNs and D2-MSNs play opposing roles in cocaine-associated behaviors. Further, cocaine induces differential adaptations in these two subpopulations in NAc, including changes to synaptic plasticity, glutamatergic signaling, and spine morphology.

Genetic Variation In OPRD1 and the Response To Treatment For Opioid Dependence With Buprenorphine In European-American Females. Clarke TK, Crist RC, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. Pharmacogenomics J. 2013. [Epub ahead of print]
Two commonly prescribed treatments for opioid addiction are methadone and buprenorphine. Although these drugs show some efficacy in treating opioid dependence, treatment response varies among individuals. It is likely that genetic factors have a role in determining treatment outcome. This study analyses the pharmacogenetic association of six polymorphisms in OPRD1, the gene encoding the delta-opioid receptor, on treatment outcome in 582 opioid addicted European Americans randomized to either methadone or buprenorphine/naloxone (Suboxone) over the course of a 24-week open-label clinical trial. Treatment outcome was assessed as the number of missed or opioid-positive urine drug screens over the 24 weeks. In the total sample, no single-nucleotide

polymorphisms (SNPs) in OPRD1 were significantly associated with treatment outcome in either treatment arm. However, sex-specific analyses revealed two intronic SNPs (rs581111 and rs529520) that predicted treatment outcome in females treated with buprenorphine. Females with the AA or AG genotypes at rs581111 had significantly worse outcomes than those with the GG genotype when treated with buprenorphine (P=0.03, relative risk (RR)=1.67, 95% confidence interval (CI) 1.06-2.1). For rs529520, females with the AA genotype had a significantly worse outcome than those with the CC genotype when (P=0.006, RR=2.15, 95% CI 1.3-2.29). No significant associations were detected in males. These findings suggest that rs581111 and rs52920 may be useful when considering treatment options for female opioid addicts, however, confirmation in an independent sample is warranted.

A Common Biological Basis Of Obesity and Nicotine Addiction. Thorgeirsson TE, Gudbjartsson DF, Sulem P, Besenbacher S, Styrkarsdottir U, Thorleifsson G, Walters GB, Furberg H, Sullivan PF, Marchini J, McCarthy MI, Steinthorsdottir V, Thorsteinsdottir U, Stefansson K. Transl Psychiatry. 2013; 3: e308.
Smoking influences body weight such that smokers weigh less than non-smokers and smoking cessation often leads to weight increase. The relationship between body weight and smoking is partly explained by the effect of nicotine on appetite and metabolism. However, the brain reward system is involved in the control of the intake of both food and tobacco. The authors evaluated the effect of single-nucleotide polymorphisms (SNPs) affecting body mass index (BMI) on smoking behavior, and tested the 32 SNPs identified in a meta-analysis for association with two smoking phenotypes, smoking initiation (SI) and the number of cigarettes smoked per day (CPD) in an Icelandic sample (N=34,216 smokers). Combined according to their effect on BMI, the SNPs correlate with both SI (r=0.019, P=0.00054) and CPD (r=0.032, P=8.0 × 10(-7)). These findings replicate in a second large data set (N=127,274, thereof 76,242 smokers) for both SI (P=1.2 × 10(-5)) and CPD (P=9.3 × 10(-5)). Notably, the variant most strongly associated with BMI (rs1558902-A in FTO) did not associate with smoking behavior. The association with smoking behavior is not due to the effect of the SNPs on BMI. These results strongly point to a common biological basis of the regulation of our appetite for tobacco and food, and thus the vulnerability to nicotine addiction and obesity.

Cocaine Self-Administration Behavior In Inbred Mouse Lines Segregating Different Capacities For Inhibitory Control. Cervantes MC, Laughlin RE, Jentsch JD. Psychopharmacology (Berl). 2013; 229(3): 515-525.
Various dimensions of impulsivity have been linked to substance abuse and dependence, both as consequences of, and as predisposing factors to addiction. With respect to the latter, they may be quantitative indicators of liability for substance use disorders (SUD) and aid in determining underlying genetic influences. The authors have previously determined that inhibitory control over impulsive responding, as measured by a reversal learning task, is heritable and under substantial genetic control, however their role as explaining variables for aspects of SUD have not been well explored. The aim of this study was to test for an association between genetically determined differences in inhibitory control and addiction-related phenotypes, such that phenotypes of poor inhibitory control would predict propensity for elevated operant drug-seeking and -taking behaviors. Mice from BxD strains with either good reversal learning (GRL) or poor reversal learning (PRL) ability were tested for intravenous cocaine self-administration under FR1, FR2, and FR5 reinforcement schedules. Additionally, locomotor responses to experimenter-delivered cocaine were assessed. Compared to GRL strains, PRL strains acquired self-administration behavior more rapidly and administered cocaine at greater rates under all schedules of reinforcement, without any

differences in discrimination index. In addition, PRL mice also exhibited increased responding during time-out periods. PRL strains also showed larger locomotor responses to 10 or 20 mg/kg injections of cocaine. These studies demonstrate that heritable strain differences in inhibitory control do influence drug self-administration, thus suggest that genetically driven impulsivity of this type may predispose susceptibility to drug abuse and addiction.

Transmission Of Chimeric HIV By Mating In Conventional Mice: Prevention By Pre-Exposure Antiretroviral Therapy and Reduced Susceptibility During Estrus. Hadas E, Chao W, He H, Saini M, Daley E, Saifuddin M, Bentsman G, Ganz E, Volsky DJ, Potash MJ. Dis Model Mech. 2013; 6(5): 1292-1298.

Heterosexual transmission accounts for the majority of new human immunodeficiency virus (HIV) cases worldwide. The current approach to investigate HIV heterosexual transmission in animals involves application of virus stock to the vaginal surface, a method that does not reproduce the physiological conditions of vaginal intercourse that influence the rate of transmission. The authors have previously described efficient infection of conventional mice using EcoHIV/NL4-3 and EcoHIV/NDK, chimeric HIV molecular clones constructed to express all HIV structural and regulatory genes except envelope, which is replaced by a rodent-tropic envelope gene. Here they investigated whether EcoHIV/NDK-infected male mice transmit virus to females during coitus, and the sensitivity of this transmission to HIV pre-exposure prophylaxis and the estrus state. Their general approach was to allow mating between EcoHIV/NDK-infected male mice and uninfected females for 1-7 nights. At 1-6 weeks after mating, mice were euthanized and virus burdens were measured by quantitative PCR (qPCR) amplification of HIV RNA or DNA in peritoneal macrophages, inguinal lymph node cells, spleen cells or vas deferens, or by ELISA for antibodies to HIV Gag. We found that 70-100% of female mice mated to EcoHIV/NDK-infected males acquired infection. Pericoital treatment of females with either 2',3'-dideoxcytidine (ddC) or tenofovir largely prevented their EcoHIV/NDK infection by mating ($P<0.05$ and $P<0.003$, respectively). In males, T cells were dispensable for virus transmission. The rate of EcoHIV/NDK sexual transmission to females in estrus declined sharply ($P=0.003$) but their infection by injection was unaffected, indicating that the local environment in the female reproductive tract influences susceptibility to HIV. The authors conclude that this system of EcoHIV/NDK transmission during mouse mating reproduces key features of heterosexual transmission of HIV in humans and can be used to investigate its biology and control.

Radionuclide Labeling and Evaluation Of Candidate Radioligands For PET Imaging Of Histone Deacetylase In the Brain. Seo YJ, Muench L, Reid A, Chen J, Kang Y, Hooker JM, Volkow ND, Fowler JS, Kim SW. Bioorg Med Chem Lett. 2013 [Epub ahead of print].

Histone deacetylases (HDACs) regulate gene expression by inducing conformational changes in chromatin. Ever since the discovery of a naturally occurring HDAC inhibitor, trichostatin A (TSA) stimulated the recent development of suberoylanilide (SAHA, Zolinza®), HDAC has become an important molecular target for drug development. This has created the need to develop specific in vivo radioligands to study epigenetic regulation and HDAC engagement for drug development for diseases including cancer and psychiatric disorders. 6-([^{18}F]Fluoro acetamido)-1-hexanoicanilide ([^{18}F]FAHA) was recently developed as a HDAC substrate and shows moderate blood-brain barrier (BBB) permeability and specific signal (by metabolic trapping/or deacetylation) but rapid metabolism. Here, the authors report the radiosynthesis of two carbon-11 labeled candidate radiotracers (substrate- and inhibitor-based radioligand) for HDAC and their evaluation in non-human primate brain. PET studies showed very low brain uptake and rapid metabolism of both labeled compounds but revealed a surprising enhancement of brain penetration by F for H

substitution when comparing one of these to [^{18}F]FAHA. Further structural refinement is needed for the development of brain-penetrant, metabolically stable HDAC radiotracers and to understand the role of fluorine substitution on brain penetration.

ΔFosB Induction in Striatal Medium Spiny Neuron Subtypes in Response to Chronic Pharmacological, Emotional, and Optogenetic Stimuli. Lobo MK, Zaman S, Damez-Werno DM, Koo JW, Bagot RC, Dinieri JA, Nugent A, Finkel E, Chaudhury D, Chandra R, Riberio E, Rabkin J, Mouzon E, Cachope R, Cheer JF, Han MH, Dietz DM, Self DW, Hurd YL, Vialou V, Nestler EJ. J Neurosci. 2013; 33(47): 18381-18395.
The transcription factor, ΔFosB, is robustly and persistently induced in striatum by several chronic stimuli, such as drugs of abuse, antipsychotic drugs, natural rewards, and stress. However, very few studies have examined the degree of ΔFosB induction in the two striatal medium spiny neuron (MSN) subtypes. The authors make use of fluorescent reporter BAC transgenic mice to evaluate induction of ΔFosB in dopamine receptor 1 (D1) enriched and dopamine receptor 2 (D2) enriched MSNs in ventral striatum, nucleus accumbens (NAc) shell and core, and in dorsal striatum (dStr) after chronic exposure to several drugs of abuse including cocaine, ethanol, Δ(9)-tetrahydrocannabinol, and opiates; the antipsychotic drug, haloperidol; juvenile enrichment; sucrose drinking; calorie restriction; the serotonin selective reuptake inhibitor antidepressant, fluoxetine; and social defeat stress. Their findings demonstrate that chronic exposure to many stimuli induces ΔFosB in an MSN-subtype selective pattern across all three striatal regions. To explore the circuit-mediated induction of ΔFosB in striatum, the authors use optogenetics to enhance activity in limbic brain regions that send synaptic inputs to NAc; these regions include the ventral tegmental area and several glutamatergic afferent regions: medial prefrontal cortex, amygdala, and ventral hippocampus. These optogenetic conditions lead to highly distinct patterns of ΔFosB induction in MSN subtypes in NAc core and shell. Together, these findings establish selective patterns of ΔFosB induction in striatal MSN subtypes in response to chronic stimuli and provide novel insight into the circuit-level mechanisms of ΔFosB induction in striatum.

Controlled-Deactivation Cannabinergic Ligands. Sharma R, Nikas SP, Paronis CA, Wood JT, Halikhedkar A, Guo JJ, Thakur GA, Kulkarni S, Benchama O, Raghav JG, Gifford RS, Jarbe TU, Bergman J, Makriyannis A. J Med Chem. 2013.
The authors report an approach for obtaining novel cannabinoid analogs with controllable deactivation and improved druggability. Their design involves the incorporation of a metabolically labile ester group at the 2'-position on a series of (-)-D8-THC analogs. They have sought to introduce benzylic substituents alpha to the ester group which affect the half-lives of deactivation through enzymatic activity while enhancing the affinities and efficacies of individual ligands for the CB1 and CB2 receptors. The 1'-(S)-methyl, 1'-gem-dimethyl and 1'-cyclobutyl analogs exhibit remarkably high affinities for both CB receptors. The novel ligands are susceptible to enzymatic hydrolysis by plasma esterases in a controllable manner while their metabolites are inactive at the CB receptors. In further in vitro and in vivo experiments key analogs were shown to be potent CB1 receptor agonists and exhibit CB1-mediated hypothermic and analgesic effects.

Role of FAAH-Like Anandamide Transporter in Anandamide Inactivation. Leung K, Elmes MW, Glaser ST, Deutsch DG, Kaczocha M. Plos One. 2013; 8(11): e79355.
The endocannabinoid system modulates numerous physiological processes including nociception and reproduction. Anandamide (AEA) is an endocannabinoid that is inactivated by cellular uptake followed by intracellular hydrolysis by fatty acid amide hydrolase (FAAH). Recently, FAAH-like anandamide transporter (FLAT), a truncated and catalytically-inactive variant of FAAH, was

proposed to function as an intracellular AEA carrier and mediate its delivery to FAAH for hydrolysis. Pharmacological inhibition of FLAT potentiated AEA signaling and produced antinociceptive effects. Given that endocannabinoids produce analgesia through central and peripheral mechanisms, the goal of the current work was to examine the expression of FLAT in the central and peripheral nervous systems. In contrast to the original report characterizing FLAT, expression of FLAT was not observed in any of the tissues examined. To investigate the role of FLAT as a putative AEA binding protein, FLAT was generated from FAAH using polymerase chain reaction and further analyzed. Despite its low cellular expression, FLAT displayed residual catalytic activity that was sensitive to FAAH inhibitors and abolished following mutation of its catalytic serine. Overexpression of FLAT potentiated AEA cellular uptake and this appeared to be dependent upon its catalytic activity. Immunofluorescence revealed that FLAT localizes primarily to intracellular membranes and does not contact the plasma membrane, suggesting that its capability to potentiate AEA uptake may stem from its enzymatic rather than transport activity. Collectively, our data demonstrate that FLAT does not serve as a global intracellular AEA carrier, although a role in mediating localized AEA inactivation in mammalian tissues cannot be ruled out.

Spinal Mitochondrial-Derived Peroxynitrite Enhances Neuroimmune Activation During Morphine Hyperalgesia and Antinociceptive Tolerance. Little JW, Cuzzocrea S, Bryant L, Esposito E, Doyle T, Rausaria S, Neumann WL, Salvemini D. Pain. 2013; 154(7): 978-986.
Treatment of severe pain by morphine, the gold-standard opioid and a potent drug in our arsenal of analgesic medications, is limited by the eventual development of hyperalgesia and analgesic tolerance. The authors recently reported that systemic administration of a peroxynitrite (PN) decomposition catalyst (PNDC) or superoxide dismutase mimetic attenuates morphine hyperalgesia and antinociceptive tolerance and reduces PN-mediated mitochondrial nitroxidative stress in the spinal cord. These results suggest the potential involvement of spinal PN signaling in this setting; which was examined in the present study. PN removal with intrathecal delivery of manganese porphyrin-based dual-activity superoxide/PNDCs, MnTE-2-PyP(5+) and the more lipophilic MnTnHex-2-PyP(5+), blocked hyperalgesia and antinociceptive tolerance in rats. Noteworthy is that intrathecal MnTnHex-2-PyP(5+) prevented nitration and inactivation of mitochondrial manganese superoxide dismutase. Mitochondrial manganese superoxide dismutase inactivation enhances the superoxide-to-PN pathway by preventing the dismutation of superoxide to hydrogen peroxide, thus providing an important enzymatic source for PN formation. Additionally, intrathecal MnTnHex-2-PyP(5+) attenuated neuroimmune activation by preventing the activation of nuclear factor kappa B, extracellular-signal-regulated kinase and p38 mitogen activated protein kinases, and the enhanced levels of proinflammatory cytokines, interleukin (IL)-1β and IL-6, while increasing anti-inflammatory cytokines, IL-4 and IL-10. The role of PN was further confirmed using intrathecal or oral delivery of the superoxide-sparing PNDC, SRI-110. These results suggest that mitochondrial-derived PN triggers the activation of several biochemical pathways engaged in the development of neuroinflammation in the spinal cord that are critical to morphine hyperalgesia and tolerance, further supporting the potential of targeting PN as an adjunct to opiates to maintain pain relief.

Cocaine Exposure Enhances Permissiveness Of Quiescent T Cells To HIV Infection. Kim SG, Jung JB, Dixit D, Rovner R Jr, Zack JA, Baldwin GC, Vatakis DN. J Leukoc Biol. 2013 Oct; 94(4): 835-843. doi: 10.1189/jlb.1112566. Epub 2013 Jul 1.
In vivo and in vitro exposure to stimulants has been associated with increased levels of HIV infection in PBMCs. Among these lymphocyte subsets, quiescent CD4(+) T cells make up the majority of circulating T cells in the blood. Others and the present authors have demonstrated that

HIV infects this population of cells inefficiently. However, minor changes in their cell state can render them permissive to infection, significantly impacting the viral reservoir. The authors have hypothesized that stimulants, such as cocaine, may perturb the activation state of quiescent cells enhancing permissiveness to infection. Quiescent T cells isolated from healthy human donors were exposed to cocaine and infected with HIV. Samples were harvested at different time-points to assess the impact of cocaine on their susceptibility to infection at various stages of the HIV life cycle. These data show that a 3-day exposure to cocaine enhanced infection of quiescent cells, an effect that appears to be mediated by σ1R and D4R. Overall, these results indicate that cocaine-mediated effects on quiescent T cells may increase the pool of infection-susceptible T cells. The latter underscores the impact that stimulants have on HIV-seropositive individuals and the challenges posed for treatment.

Morphine Induced Exacerbation Of Sepsis Is Mediated By Tempering Endotoxin Tolerance Through Modulation Of Mir-146a. Banerjee S, Meng J, Das S, Krishnan A, Haworth J, Charboneau R, Zeng Y, Ramakrishnan S, Roy S. Sci Rep. 2013; 3: 1977. doi: 10.1038/srep01977.
Development of tolerance to endotoxin prevents sustained hyper inflammation during systemic infections. Here the authors report for the first time that chronic morphine treatment tempers endotoxin tolerance resulting in persistent inflammation, septicemia and septic shock. Morphine was found to down-regulate endotoxin/LPS induced miR-146a and 155 in macrophages. However, only miR-146a over expression, but not miR-155 abrogates morphine mediated hyper-inflammation. Conversely, antagonizing miR-146a (but not miR-155) heightened the severity of morphine-mediated hyper-inflammation. These results suggest that miR-146a acts as a molecular switch controlling hyper-inflammation in clinical and/or recreational use of morphine.

Bivalent Ligands That Target μ Opioid (MOP) and Cannabinoid1 (CB1) Receptors Are Potent Analgesics Devoid of Tolerance. Le Naour M, Akgün E, Yekkirala A, Lunzer MM, Powers MD, Kalyuzhny AE, Portoghese PS. J Med Chem. 2013: [Epub ahead of print].
Given that μ opioid (MOP) and canabinoid (CB1) receptors are colocalized in various regions of the central nervous system and have been reported to associate as heteromer (MOP-CB1) in cultured cells, the possibility of functional, endogenous MOP-CB1 in nociception and other pharmacologic effects has been raised. As a first step in investigating this possibility, the authors have synthesized a series of bivalent ligands 1-5 that contain both μ agonist and CB1 antagonist pharmacophores for use as tools to study the functional interaction between MOP and CB1 receptors in vivo. Immunofluorescent studies on HEK293 cells coexpressing both receptors suggested 5 (20-atom spacer) to be the only member of the series that bridges the protomers of the heteromer. Antinociceptive testing in mice revealed 5 to be the most potent member of the series. As neither a mixture of monovalent ligands 9 + 10 nor bivalents 2-5 produced tolerance in mice, MOR-CB1 apparently is not an important target for reducing tolerance.

Two Novel Mutations in ABHD12: Expansion of the Mutation Spectrum in PHARC and Assessment of Their Functional Effects. Chen DH, Naydenov A, Blankman JL, Mefford HC, Davis M, Sul Y, Barloon AS, Bonkowski E, Wolff J, Matsushita M, Smith C, Cravatt BF, Mackie K, Raskind WH, Stella N, Bird TD. Hum Mutat. 2013; 34(12): 1672-1678.
PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataracts) is a recently described autosomal-recessive neurodegenerative disease caused by mutations in the α-β-hydrolase domain-containing 12 gene (ABHD12). Only five homozygous ABHD12 mutations have been reported and the pathogenesis of PHARC remains unclear. The authors evaluated a woman who manifested short stature as well as the typical features of PHARC. Sequence analysis of ABHD12

revealed a novel heterozygous c.1129A>T (p.Lys377*) mutation. Targeted comparative genomic hybridization detected a 59-kb deletion that encompasses exon 1 of ABHD12 and exons 1-4 of an adjacent gene, GINS1, and includes the promoters of both genes. The heterozygous deletion was also carried by the patient's asymptomatic mother. Quantitative reverse transcription-PCR demonstrated ~50% decreased expression of ABHD12 RNA in lymphoblastoid cell lines from both individuals. Activity-based protein profiling of serine hydrolases revealed absence of ABHD12 hydrolase activity in the patient and 50% reduction in her mother. This is the first report of compound heterozygosity in PHARC and the first study to describe how a mutation might affect ABHD12 expression and function. The possible involvement of haploinsufficiency for GINS1, a DNA replication complex protein, in the short stature of the patient and her mother requires further studies.

Ligands That Interact With Putative MOR-Mglur5 Heteromer In Mice With Inflammatory Pain Produce Potent Antinociception. Akgün E, Javed MI, Lunzer MM, Smeester BA, Beitz AJ, Portoghese PS. Proc Natl Acad Sci U S A. 2013; 110(28): 11595-11599.
The low effectiveness of morphine and related mu opioid analgesics for the treatment of chronic inflammatory pain is a result of opioid-induced release of proinflammatory cytokines and glutamate that lower the pain threshold. In this regard, the use of opioids with metabotropic glutamate-5 receptor (mGluR5) antagonist has been reported to increase the efficacy of morphine and prevent the establishment of adverse effects during chronic use. Given the presence of opioid receptors (MORs) and mGluR5 in glia and neurons, together with reports that suggest coexpressed MOR/mGluR5 receptors in cultured cells associate as a heteromer, the possibility that such a heteromer could be a target in vivo was addressed by the design and synthesis of a series of bivalent ligands that contain mu opioid agonist and mGluR5 antagonist pharmacophores linked through spacers of varying length (10-24 atoms). The series was evaluated for antinociception using the tail-flick and von Frey assays in mice pretreated with lipopoly-saccharide (LPS) or in mice with bone cancer. In LPS-pretreated mice, MMG22 (4c, 22-atom spacer) was the most potent member of the series (intrathecal ED50 ~9 fmol per mouse), whereas in untreated mice its ED50 was more than three orders of magnitude higher. As members of the series with shorter or longer spacers have ≥500-fold higher ED50s in LPS-treated mice, the exceptional potency of MMG22 may be a result of the optimal bridging of protomers in a putative MOR-mGluR5 heteromer. The finding that MMG22 possesses a >10(6) therapeutic ratio suggests that it may be an excellent candidate for treatment of chronic, intractable pain via spinal administration.

Identification Of A M-Δ Opioid Receptor Heteromer-Biased Agonist With Antinociceptive Activity. Gomes I, Fujita W, Gupta A, Saldanha AS, Negri A, Pinello CE, Roberts E, Filizola M, Hodder P, Devi LA. Proc Natl Acad Sci U S A. 2013; 110(29): 12072-12077.
G protein-coupled receptors play a pivotal role in many physiological signaling pathways. Mounting evidence suggests that G protein-coupled receptors, including opioid receptors, form dimers, and dimerization is necessary for receptor maturation, signaling, and trafficking. However, the physiological role of dimerization in vivo has not been well-explored because of the lack of tools to study these dimers in endogenous systems. To address this problem, the authors previously generated antibodies to μ-δ opioid receptor (μOR-δOR) dimers and used them to study the pharmacology and signaling by this heteromer. They also showed that the heteromer exhibits restricted distribution in the brain and that its abundance is increased in response to chronic morphine administration. Thus, the μOR-δOR heteromer represents a potentially unique target for the development of therapeutics to treat pain. Here, the authors report the identification of compounds targeting μOR-δOR heteromers through high-throughput screening of a small-molecule

library. These compounds exhibit activity in μOR-δOR cells but not μOR or δOR cells alone. Among them, CYM51010 was found to be a μOR-δOR-biased ligand, because its activity is blocked by the μOR-δOR heteromer antibody. Notably, systemic administration of CYM51010 induced antinociceptive activity similar to morphine, and chronic administration of CYM51010 resulted in lesser antinociceptive tolerance compared with morphine. Taken together, these results suggest that CYM51010, a μOR-δOR-biased ligand, could serve as a scaffold for the development of a unique type (heteromer-biased) of drug that is more potent and without the severe side effects associated with conventional clinical opioids.

Truncation Of the Peptide Sequence In Bifunctional Ligands With Mu and Delta Opioid Receptor Agonist and Neurokinin 1 Receptor Antagonist Activities. Nair P, Yamamoto T, Largent-Milnes TM, Cowell S, Kulkarni V, Moye S, Navratilova E, Davis P, Ma SW, Vanderah TW, Lai J, Porreca F, Hruby VJ. Bioorg Med Chem Lett. 2013 Sep 1; 23(17): 4975-4978.
The optimization and truncation of the authors' lead peptide-derived ligand TY005 possessing eight amino-acid residues was performed. Among the synthesized derivatives, NP30 (Tyr(1)-DAla(2)-Gly(3)-Phe(4)-Gly(5)-Trp(6)-O-[3',5'-Bzl(CF3)2]) showed balanced and potent opioid agonist as well as substance P antagonist activities in isolated tissue-based assays, together with significant antinociceptive and antiallodynic activities in vivo.

Exploring the Nicotinic Acetylcholine Receptor-Associated Proteome With iTRAQ and Transgenic Mice. McClure-Begley TD, Stone KL, Marks MJ, Grady SR, Colangelo CM, Lindstrom JM, Picciotto MR. Genomics Proteomics Bioinformatics 2013; 11(4): 207-218.
Neuronal nicotinic acetylcholine receptors (nAChRs) containing α4 and β2 subunits are the principal receptors in the mammalian central nervous system that bind nicotine with high affinity. These nAChRs are involved in nicotine dependence, mood disorders, neurodegeneration and neuroprotection. However, our understanding of the interactions between α4β2-containing (α4β2(∗)) nAChRs and other proteins remains limited. In this study, the authors identified proteins that interact with α4β2(∗) nAChRs in a genedose dependent pattern by immunopurifying β2(∗) nAChRs from mice that differ in α4 and β2 subunit expression and performing proteomic analysis using isobaric tags for relative and absolute quantitation (iTRAQ). Reduced expression of either the α4 or the β2 subunit results in a correlated decline in the expression of a number of putative interacting proteins. The authors identified 208 proteins co-immunoprecipitated with these nAChRs. Furthermore, stratified linear regression analysis indicated that levels of 17 proteins was correlated significantly with expression of α4β2 nAChRs, including proteins involved in cytoskeletal rearrangement and calcium signaling. These findings represent the first application of quantitative proteomics to produce a β2(∗) nAChR interactome and describe a novel technique used to discover potential targets for pharmacological manipulation of α4β2 nAChRs and their downstream signaling mechanisms.

Select G-Protein-Coupled Receptors Modulate Agonist-Induced Signaling via a ROCK, LIMK, and *-Arrestin 1 Pathway. Mittal N, Roberts K, Pal K, Bentolila LA, Fultz E, Minasyan A, Cahill C, Pradhan A, Conner D, Defea K, Evans C, Walwyn W. Cell Rep 2013.
G-protein-coupled receptors (GPCRs) are typically present in a basal, inactive state but, when bound to an agonist, activate downstream signaling cascades. In studying arrestin regulation of opioid receptors in dorsal root ganglia (DRG) neurons, the authors find that agonists of delta opioid receptors (δORs) activate cofilin through Rho-associated coiled-coil-containing protein kinase (ROCK), LIM domain kinase (LIMK), and β-arrestin 1 (β-arr1) to regulate actin polymerization. This controls receptor function, as assessed by agonist-induced inhibition of voltage-dependent

Ca(2+) channels in DRGs. Agonists of opioid-receptor-like receptors (ORL1) similarly influence the function of this receptor through ROCK, LIMK, and β-arr1. Functional evidence of this cascade was demonstrated in vivo, where the behavioral effects of δOR or ORL1 agonists were enhanced in the absence of β-arr1 or prevented by inhibiting ROCK. This pathway allows δOR and ORL1 agonists to rapidly regulate receptor function.

Nanometre-Scale Thermometry In A Living Cell. Kucsko G, Maurer PC, Yao NY, Kubo M, Noh HJ, Lo PK, Park H, Lukin MD. Nature 2013; 500(7460): 54-58.
Sensitive probing of temperature variations on nanometre scales is an outstanding challenge in many areas of modern science and technology. In particular, a thermometer capable of subdegree temperature resolution over a large range of temperatures as well as integration within a living system could provide a powerful new tool in many areas of biological, physical and chemical research. Possibilities range from the temperature-induced control of gene expression and tumour metabolism to the cell-selective treatment of disease and the study of heat dissipation in integrated circuits. By combining local light-induced heat sources with sensitive nanoscale thermometry, it may also be possible to engineer biological processes at the subcellular level. Here the authors demonstrate a new approach to nanoscale thermometry that uses coherent manipulation of the electronic spin associated with nitrogen-vacancy colour centres in diamond. Their technique makes it possible to detect temperature variations as small as 1.8mK (a sensitivity of 9mKHz(-1/2)) in an ultrapure bulk diamond sample. Using nitrogen-vacancy centres in diamond nanocrystals (nanodiamonds), the authors directly measure the local thermal environment on length scales as short as 200nanometres. Finally, by introducing both nanodiamonds and gold nanoparticles into a single human embryonic fibroblast, they demonstrate temperature-gradient control and mapping at the subcellular level, enabling unique potential applications in life sciences.

A Disinhibitory Microcircuit Initiates Critical-Period Plasticity In the Visual Cortex. Kuhlman SJ, Olivas ND, Tring E, Ikrar T, Xu X, Trachtenberg JT. Nature 2013; 501(7468): 543-546.
Early sensory experience instructs the maturation of neural circuitry in the cortex. This has been studied extensively in the primary visual cortex, in which loss of vision to one eye permanently degrades cortical responsiveness to that eye, a phenomenon known as ocular dominance plasticity (ODP). Cortical inhibition mediates this process, but the precise role of specific classes of inhibitory neurons in ODP is controversial. Here, the authors report that evoked firing rates of binocular excitatory neurons in the primary visual cortex immediately drop by half when vision is restricted to one eye, but gradually return to normal over the following twenty-four hours, despite the fact that vision remains restricted to one eye. This restoration of binocular-like excitatory firing rates after monocular deprivation results from a rapid, although transient, reduction in the firing rates of fast-spiking, parvalbumin-positive (PV) interneurons, which in turn can be attributed to a decrease in local excitatory circuit input onto PV interneurons. This reduction in PV-cell-evoked responses after monocular lid suture is restricted to the critical period for ODP and appears to be necessary for subsequent shifts in excitatory ODP. Pharmacologically enhancing inhibition at the time of sight deprivation blocks ODP and, conversely, pharmacogenetic reduction of PV cell firing rates can extend the critical period for ODP. These findings define the microcircuit changes initiating competitive plasticity during critical periods of cortical development. Moreover, they show that the restoration of evoked firing rates of layer 2/3 pyramidal neurons by PV-specific disinhibition is a key step in the progression of ODP.

Human MX2 Is An Interferon-Induced Post-Entry Inhibitor Of HIV-1 Infection. Goujon C, Moncorge O, Bauby H, Doyle T, Ward CC, Schaller T, Hue S, Barclay WS, Schulz R, Malim MH. Nature 2013; 502(7472): 559-562.
Animal cells harbour multiple innate effector mechanisms that inhibit virus replication. For the pathogenic retrovirus human immunodeficiency virus type 1 (HIV-1), these include widely expressed restriction factors, such as APOBEC3 proteins, TRIM5-α, BST2 (refs 4, 5) and SAMHD1 (refs 6, 7), as well as additional factors that are stimulated by type 1 interferon (IFN). Here the authors use both ectopic expression and gene-silencing experiments to define the human dynamin-like, IFN-induced myxovirus resistance 2 (MX2, also known as MXB) protein as a potent inhibitor of HIV-1 infection and as a key effector of IFN-α-mediated resistance to HIV-1 infection. MX2 suppresses infection by all HIV-1 strains tested, has equivalent or reduced effects on divergent simian immunodeficiency viruses, and does not inhibit other retroviruses such as murine leukaemia virus. The Capsid region of the viral Gag protein dictates susceptibility to MX2, and the block to infection occurs at a late post-entry step, with both the nuclear accumulation and chromosomal integration of nascent viral complementary DNA suppressed. Finally, human MX1 (also known as MXA), a closely related protein that has long been recognized as a broadly acting inhibitor of RNA and DNA viruses, including the orthomyxovirus influenza A virus, does not affect HIV-1, whereas MX2 is ineffective against influenza virus. MX2 is therefore a cell-autonomous, anti-HIV-1 resistance factor whose purposeful mobilization may represent a new therapeutic approach for the treatment of HIV/AIDS.

Genetic Identification Of A Neural Circuit That Suppresses Appetite. Carter ME, Soden ME, Zweifel LS, Palmiter RD. Nature 2013; 503(7474): 111-114.
Appetite suppression occurs after a meal and in conditions when it is unfavourable to eat, such as during illness or exposure to toxins. A brain region proposed to play a role in appetite suppression is the parabrachial nucleus, a heterogeneous population of neurons surrounding the superior cerebellar peduncle in the brainstem. The parabrachial nucleus is thought to mediate the suppression of appetite induced by the anorectic hormones amylin and cholecystokinin, as well as by lithium chloride and lipopolysaccharide, compounds that mimic the effects of toxic foods and bacterial infections, respectively. Hyperactivity of the parabrachial nucleus is also thought to cause starvation after ablation of orexigenic agouti-related peptide neurons in adult mice. However, the identities of neurons in the parabrachial nucleus that regulate feeding are unknown, as are the functionally relevant downstream projections. Here the authors identify calcitonin gene-related peptide-expressing neurons in the outer external lateral subdivision of the parabrachial nucleus that project to the laterocapsular division of the central nucleus of the amygdala as forming a functionally important circuit for suppressing appetite. Using genetically encoded anatomical, optogenetic and pharmacogenetic tools, they demonstrate that activation of these neurons projecting to the central nucleus of the amygdala suppresses appetite. In contrast, inhibition of these neurons increases food intake in circumstances when mice do not normally eat and prevents starvation in adult mice whose agouti-related peptide neurons are ablated. Taken together, these data demonstrate that this neural circuit from the parabrachial nucleus to the central nucleus of the amygdala mediates appetite suppression in conditions when it is unfavourable to eat. This neural circuit may provide targets for therapeutic intervention to overcome or promote appetite.

Prolonged Dopamine Signalling In Striatum Signals Proximity and Value Of Distant Rewards. vHowe MW, Tierney PL, Sandberg SG, Phillips PEM, Graybiel AM. Nature 2013; 500(7464): 575-579.
Predictions about future rewarding events have a powerful influence on behaviour. The phasic spike activity of dopamine-containing neurons, and corresponding dopamine transients in the striatum, are thought to underlie these predictions, encoding positive and negative reward prediction errors. However, many behaviours are directed towards distant goals, for which transient signals may fail to provide sustained drive. Here the authors report an extended mode of reward-predictive dopamine signalling in the striatum that emerged as rats moved towards distant goals. These dopamine signals, which were detected with fast-scan cyclic voltammetry (FSCV), gradually increased or--in rare instances--decreased as the animals navigated mazes to reach remote rewards, rather than having phasic or steady tonic profiles. These dopamine increases (ramps) scaled flexibly with both the distance and size of the rewards. During learning, these dopamine signals showed spatial preferences for goals in different locations and readily changed in magnitude to reflect changing values of the distant rewards. Such prolonged dopamine signalling could provide sustained motivational drive, a control mechanism that may be important for normal behaviour and that can be impaired in a range of neurologic and neuropsychiatric disorders.

A Prolyl-Isomerase Mediates Dopamine-Dependent Plasticity and Cocaine Motor Sensitization. Park JM, Hu JH, Milshteyn A, Zhang PW, Moore CG, Park S, Datko MC, Domingo RD, Reyes CM, Wang XJ, Etzkorn FA, Xiao B, Szumlinski KK, Kern D, Linden DJ, Worley PF. Cell 2013: 154(3): 637-650.
Synaptic plasticity induced by cocaine and other drugs underlies addiction. Here the authors elucidate molecular events at synapses that cause this plasticity and the resulting behavioral response to cocaine in mice. In response to D1-dopamine-receptor signaling that is induced by drug administration, the glutamate-receptor protein metabotropic glutamate receptor 5 (mGluR5) is phosphorylated by microtubule-associated protein kinase (MAPK), which the authors show potentiates Pin1-mediated prolyl-isomerization of mGluR5 in instances where the product of an activity-dependent gene, Homer1a, is present to enable Pin1-mGluR5 interaction. These biochemical events potentiate N-methyl-D-aspartate receptor (NMDAR)-mediated currents that underlie synaptic plasticity and cocaine-evoked motor sensitization as tested in mice with relevant mutations. The findings elucidate how a coincidence of signals from the nucleus and the synapse can render mGluR5 accessible to activation with consequences for drug-induced dopamine responses and point to depotentiation at corticostriatal synapses as a possible therapeutic target for treating addiction.

Beclin 2 Functions In Autophagy, Degradation Of G Protein-Coupled Receptors, and Metabolism. He C, Wei Y, Sun K, Li B, Dong X, Zou Z, Liu Y, Kinch LN, Khan S, Sinha S, Xavier RJ, Grishin NV, Xiao G, Eskelinen EL, Scherer PE, Whistler JL, Levine B. Cell 2013; 154(5): 1085-1099.
The molecular mechanism of autophagy and its relationship to other lysosomal degradation pathways remain incompletely understood. Here, the authors identified a previously uncharacterized mammalian-specific protein, Beclin 2, which, like Beclin 1, functions in autophagy and interacts with class III PI3K complex components and Bcl-2. However, Beclin 2, but not Beclin 1, functions in an additional lysosomal degradation pathway. Beclin 2 is required for ligand-induced endolysosomal degradation of several G protein-coupled receptors (GPCRs) through its interaction with GASP1. Beclin 2 homozygous knockout mice have decreased embryonic viability, and heterozygous knockout mice have defective autophagy, increased levels of brain cannabinoid 1

receptor, elevated food intake, and obesity and insulin resistance. The authors' findings identify Beclin 2 as a converging regulator of autophagy and GPCR turnover and highlight the functional and mechanistic diversity of Beclin family members in autophagy, endolysosomal trafficking, and metabolism.

The Inhibitory Circuit Architecture Of the Lateral Hypothalamus Orchestrates Feeding. Jennings JH, Rizzi G, Stamatakis AM, Ung RL, Stuber GD. Science 2013; 341(6153): 1517-1521.
The growing prevalence of overeating disorders is a key contributor to the worldwide obesity epidemic. Dysfunction of particular neural circuits may trigger deviations from adaptive feeding behaviors. The lateral hypothalamus (LH) is a crucial neural substrate for motivated behavior, including feeding, but the precise functional neurocircuitry that controls LH neuronal activity to engage feeding has not been defined. The authors observed that inhibitory synaptic inputs from the extended amygdala preferentially innervate and suppress the activity of LH glutamatergic neurons to control food intake. These findings help explain how dysregulated activity at a number of unique nodes can result in a cascading failure within a defined brain network to produce maladaptive feeding.

Constitutive μ-Opioid Receptor Activity Leads To Long-Term Endogenous Analgesia and Dependence. Corder G, Doolen S, Donahue RR, Winter MK, Jutras BL, He Y, Hu X, Wieskopf JS, Mogil JS, Storm DR, Wang ZJ, McCarson KE, Taylor BK. Science 2013; 341(6152): 1394-1399.
Opioid receptor antagonists increase hyperalgesia in humans and animals, which indicates that endogenous activation of opioid receptors provides relief from acute pain; however, the mechanisms of long-term opioid inhibition of pathological pain have remained elusive. The authors found that tissue injury produced μ-opioid receptor (MOR) constitutive activity (MOR(CA)) that repressed spinal nociceptive signaling for months. Pharmacological blockade during the posthyperalgesia state with MOR inverse agonists reinstated central pain sensitization and precipitated hallmarks of opioid withdrawal (including adenosine 3',5'-monophosphate overshoot and hyperalgesia) that required N-methyl-D-aspartate receptor activation of adenylyl cyclase type 1. Thus, MOR(CA) initiates both analgesic signaling and a compensatory opponent process that generates endogenous opioid dependence. Tonic MOR(CA) suppression of withdrawal hyperalgesia may prevent the transition from acute to chronic pain.

Micro- and Nanoscale Devices For the Investigation Of Epigenetics and Chromatin Dynamics. Aguilar CA, Craighead HG. Nat Nanotechnol 2013; 8(10): 709-718.
Deoxyribonucleic acid (DNA) is the blueprint on which life is based and transmitted, but the way in which chromatin - a dynamic complex of nucleic acids and proteins - is packaged and behaves in the cellular nucleus has only begun to be investigated. Epigenetic modifications sit 'on top of' the genome and affect how DNA is compacted into chromatin and transcribed into ribonucleic acid (RNA). The packaging and modifications around the genome have been shown to exert significant influence on cellular behaviour and, in turn, human development and disease. However, conventional techniques for studying epigenetic or conformational modifications of chromosomes have inherent limitations and, therefore, new methods based on micro- and nanoscale devices have been sought. Here, the authors review the development of these devices and explore their use in the study of DNA modifications, chromatin modifications and higher-order chromatin structures.

Strategic Addition Of An N-Linked Glycan To A Monoclonal Antibody Improves Its HIV-1-Neutralizing Activity. Song R, Oren DA, Franco D, Seaman MS, Ho DD. Nat Biotechnol 2013; 31(11): 1047-1052.
Ibalizumab is a humanized monoclonal antibody that binds human CD4-a key receptor for HIV-and blocks HIV-1 infection. However, HIV-1 strains with mutations resulting in loss of an N-linked glycan from the V5 loop of the envelope glycoprotein gp120 are resistant to ibalizumab. Previous structural analysis suggests that this glycan fills a void between the gp120 V5 loop and the ibalizumab light chain, perhaps causing steric hindrance that disrupts viral entry. If this void contributes to HIV-1 resistance to ibalizumab, the authors reasoned that 'refilling' it by engineering an N-linked glycan into the ibalizumab light chain at a position spatially proximal to gp120 V5 may restore susceptibility to ibalizumab. Indeed, one such ibalizumab variant neutralized 100% of 118 diverse HIV-1 strains tested in vitro, including 10 strains resistant to parental ibalizumab. These findings demonstrate that the strategic placement of a glycan in the variable region of a monoclonal antibody can substantially enhance its activity.

Opening The Black Box: Dopamine, Predictions, and Learning. Eshel N, Tian J, Uchida N. Trends Cogn Sci 2013; 17(9): 430-431.
Dopamine neurons are thought to promote learning by signaling prediction errors, that is, the difference between actual and expected outcomes. Whether these signals are sufficient for associative learning, however, remains untested. A recent study used optogenetics in a classic behavioral paradigm to confirm the role of dopamine prediction errors in learning.

Maturation Of Silent Synapses In Amygdala-Accumbens Projection Contributes To Incubation Of Cocaine Craving. Lee BR, Ma YY, Huang YH, Wang X, Otaka M, Ishikawa M, Neumann PA, Graziane NM, Brown TE, Suska A, Guo C, Lobo MK, Sesack SR, Wolf ME, Nestler EJ, Shaham Y, Schluter OM, Dong Y. Nat Neurosci 2013; 16(11): 1644-1651.
In rat models of drug relapse and craving, cue-induced cocaine seeking progressively increases after withdrawal from the drug. This 'incubation of cocaine craving' is partially mediated by time-dependent adaptations at glutamatergic synapses in nucleus accumbens (NAc). However, the circuit-level adaptations mediating this plasticity remain elusive. The authors studied silent synapses, often regarded as immature synapses that express stable NMDA receptors with AMPA receptors being either absent or labile, in the projection from the basolateral amygdala to the NAc in incubation of cocaine craving. Silent synapses were detected in this projection during early withdrawal from cocaine. As the withdrawal period progressed, these silent synapses became unsilenced, a process that involved synaptic insertion of calcium-permeable AMPA receptors (CP-AMPARs). In vivo optogenetic stimulation-induced downregulation of CP-AMPARs at amygdala-to-NAc synapses, which re-silenced some of the previously silent synapses after prolonged withdrawal, decreased incubation of cocaine craving. These findings indicate that silent synapse-based reorganization of the amygdala-to-NAc projection is critical for persistent cocaine craving and relapse after withdrawal.

Substrate-Selective COX-2 Inhibition Decreases Anxiety Via Endocannabinoid Activation. Hermanson DJ, Hartley ND, Gamble-George J, Brown N, Shonesy BC, Kingsley PJ, Colbran RJ, Reese J, Marnett LJ, Patel S. Nat Neurosci 2013; 16(9): 1291-1298.
Augmentation of endogenous cannabinoid (eCB) signaling represents an emerging approach to the treatment of affective disorders. Cyclooxygenase-2 (COX-2) oxygenates arachidonic acid to form prostaglandins, but also inactivates eCBs in vitro. However, the viability of COX-2 as a therapeutic target for in vivo eCB augmentation has not been explored. Using medicinal chemistry and in vivo

analytical and behavioral pharmacological approaches, the authors found that COX-2 is important for the regulation of eCB levels in vivo. They used a pharmacological strategy involving substrate-selective inhibition of COX-2 to augment eCB signaling without affecting related non-eCB lipids or prostaglandin synthesis. Behaviorally, substrate-selective inhibition of COX-2 reduced anxiety-like behaviors in mice via increased eCB signaling. Their data suggest a key role for COX-2 in the regulation of eCB signaling and indicate that substrate-selective pharmacology represents a viable approach for eCB augmentation with broad therapeutic potential.

Cortical Activation Of Accumbens Hyperpolarization-Active NMDARs Mediates Aversion-Resistant Alcohol Intake. Seif T, Chang SJ, Simms JA, Gibb SL, Dadgar J, Chen BT, Harvey BK, Ron D, Messing RO, Bonci A, Hopf FW. Nat Neurosci 2013; 16(8): 1094-1100.
Compulsive drinking despite serious adverse medical, social and economic consequences is a characteristic of alcohol use disorders in humans. Although frontal cortical areas have been implicated in alcohol use disorders, little is known about the molecular mechanisms and pathways that sustain aversion-resistant intake. Here, the authors show that nucleus accumbens core (NAcore) NMDA-type glutamate receptors and medial prefrontal (mPFC) and insula glutamatergic inputs to the NAcore are necessary for aversion-resistant alcohol consumption in rats. Aversion-resistant intake was associated with a new type of NMDA receptor adaptation, in which hyperpolarization-active NMDA receptors were present at mPFC and insula but not amygdalar inputs in the NAcore. Accordingly, inhibition of Grin2c NMDA receptor subunits in the NAcore reduced aversion-resistant alcohol intake. None of these manipulations altered intake when alcohol was not paired with an aversive consequence. These results identify a mechanism by which hyperpolarization-active NMDA receptors under mPFC- and insula-to-NAcore inputs sustain aversion-resistant alcohol intake.

DNA Methylation Regulates Associative Reward Learning. Day JJ, Childs D, Guzman-Karlsson MC, Kibe M, Moulden J, Song E, Tahir A, Sweatt JD. Nat Neurosci 2013; 16(10): 1445-1452.
Reward-related memories are essential for adaptive behavior and evolutionary fitness, but they are also a core component of maladaptive brain diseases such as addiction. Reward learning requires dopamine neurons located in the ventral tegmental area (VTA), which encode relationships between predictive cues and future rewards. Recent evidence suggests that epigenetic mechanisms, including DNA methylation, are essential regulators of neuronal plasticity and experience-driven behavioral change. However, the role of epigenetic mechanisms in reward learning is poorly understood. Here the authors show that the formation of reward-related associative memories in rats upregulates key plasticity genes in the VTA, which are correlated with memory strength and associated with gene-specific changes in DNA methylation. Moreover, DNA methylation in the VTA is required for the formation of stimulus-reward associations. These results provide the first evidence that that activity-dependent methylation and demethylation of DNA is an essential substrate for the behavioral and neuronal plasticity driven by reward-related experiences.

A Long Noncoding RNA Contributes To Neuropathic Pain By Silencing Kcna2 In Primary Afferent Neurons. Zhao X, Tang Z, Zhang H, Atianjoh FE, Zhao JY, Liang L, Wang W, Guan X, Kao SC, Tiwari V, Gao YJ, Hoffman PN, Cui H, Li M, Dong X, Tao YX. Nat Neurosci 2013; 16(8): 1024-1031.
Neuropathic pain is a refractory disease characterized by maladaptive changes in gene transcription and translation in the sensory pathway. Long noncoding RNAs (lncRNAs) are emerging as new players in gene regulation, but how lncRNAs operate in the development of neuropathic pain is unclear. Here the authors identify a conserved lncRNA, named Kcna2 antisense RNA, for a voltage-

dependent potassium channel mRNA, Kcna2, in first-order sensory neurons of rat dorsal root ganglion (DRG). Peripheral nerve injury increased Kcna2 antisense RNA expression in injured DRG through activation of myeloid zinc finger protein 1, a transcription factor that binds to the Kcna2 antisense RNA gene promoter. Mimicking this increase downregulated Kcna2, reduced total voltage-gated potassium current, increased excitability in DRG neurons and produced neuropathic pain symptoms. Blocking this increase reversed nerve injury-induced downregulation of DRG Kcna2 and attenuated development and maintenance of neuropathic pain. These findings suggest endogenous Kcna2 antisense RNA as a therapeutic target for the treatment of neuropathic pain.

Bidirectional NMDA Receptor Plasticity Controls CA3 Output and Heterosynaptic Metaplasticity. Hunt DL, Puente N, Grandes P, Castillo PE. Nat Neurosci 2013; 16(8): 1049-1059.
NMDA receptors (NMDARs) are classically known as coincidence detectors for the induction of long-term synaptic plasticity and have been implicated in hippocampal CA3 cell-dependent spatial memory functions that likely rely on dynamic cellular ensemble encoding of space. The unique functional properties of both NMDARs and mossy fiber projections to CA3 pyramidal cells place mossy fiber NMDARs in a prime position to influence CA3 ensemble dynamics. By mimicking presynaptic and postsynaptic activity patterns observed in vivo, the authors found a burst timing-dependent pattern of activity that triggered bidirectional long-term NMDAR plasticity at mossy fiber-CA3 synapses in rat hippocampal slices. This form of plasticity imparts bimodal control of mossy fiber-driven CA3 burst firing and spike temporal fidelity. Moreover, the authors found that mossy fiber NMDARs mediate heterosynaptic metaplasticity between mossy fiber and associational-commissural synapses. Thus, bidirectional NMDAR plasticity at mossy fiber-CA3 synapses could substantially contribute to the formation, storage and recall of CA3 cell assembly patterns.

ReaChR: A Red-Shifted Variant Of Channelrhodopsin Enables Deep Transcranial Optogenetic Excitation. Lin JY, Knutsen PM, Muller A, Kleinfeld D, Tsien RY. Nat Neurosci 2013; 16(10): 1499-1508.
Channelrhodopsins (ChRs) are used to optogenetically depolarize neurons. The authors engineered a variant of ChR, denoted red-activatable ChR (ReaChR), that is optimally excited with orange to red light ($\lambda \sim$590-630 nm) and offers improved membrane trafficking, higher photocurrents and faster kinetics compared to existing red-shifted ChRs. Red light is less scattered by tissue and is absorbed less by blood than the blue to green wavelengths that are required by other ChR variants. The authors used ReaChR expressed in the vibrissa motor cortex to drive spiking and vibrissa motion in awake mice when excited with red light through intact skull. Precise vibrissa movements were evoked by expressing ReaChR in the facial motor nucleus in the brainstem and illumination with red light through the external auditory canal. Thus, ReaChR enables transcranial optical activation of neurons in deep brain structures without the need to surgically thin the skull, form a transcranial window or implant optical fibers.

P11 and Its Role In Depression and Therapeutic Responses To Antidepressants. Svenningsson P, Kim Y, Warner-Schmidt J, Oh YS, Greengard P. Nat Rev Neurosci 2013; 14(10): 673-680.
Studies of the multifunctional protein p11 (also known as S100A10) are shedding light on the molecular and cellular mechanisms underlying depression. Here, the authors review data implicating p11 in both the amplification of serotonergic signalling and the regulation of gene transcription. They summarize studies demonstrating that levels of p11 are regulated in depression and by antidepressant regimens and, conversely, that p11 regulates depression-like behaviours

and/or responses to antidepressants. Current and future studies of p11 may provide a molecular and cellular framework for the development of novel antidepressant therapies.

A Unique Population Of Ventral Tegmental Area Neurons Inhibits the Lateral Habenula To Promote Reward. Stamatakis AM, Jennings JH, Ung RL, Blair GA, Weinberg RJ, Neve RL, Boyce F, Mattis J, Ramakrishnan C, Deisseroth K, Stuber GD. Neuron 2013; 80(4): 1039-1053.
Lateral habenula (LHb) neurons convey aversive and negative reward conditions through potent indirect inhibition of ventral tegmental area (VTA) dopaminergic neurons. Although VTA dopaminergic neurons reciprocally project to the LHb, the electrophysiological properties and the behavioral consequences associated with selective manipulations of this circuit are unknown. Here, the authors identify an inhibitory input to the LHb arising from a unique population of VTA neurons expressing dopaminergic markers. Optogenetic activation of this circuit resulted in no detectable dopamine release in LHb brain slices. Instead, stimulation produced GABA-mediated inhibitory synaptic transmission, which suppressed the firing of postsynaptic LHb neurons in brain slices and increased the spontaneous firing rate of VTA dopaminergic neurons in vivo. Furthermore, in vivo activation of this pathway produced reward-related phenotypes that were dependent on intra-LHb GABAA receptor signaling. These results suggest that noncanonical inhibitory signaling by these hybrid dopaminergic-GABAergic neurons act to suppress LHb output under rewarding conditions.

Cortical Signals For Rewarded Actions and Strategic Exploration. Donahue CH, Seo H, Lee D. Neuron 2013; 80(1): 223-234.
In stable environments, decision makers can exploit their previously learned strategies for optimal outcomes, while exploration might lead to better options in unstable environments. Here, to investigate the cortical contributions to exploratory behavior, the authors analyzed single-neuron activity recorded from four different cortical areas of monkeys performing a matching-pennies task and a visual search task, which encouraged and discouraged exploration, respectively. The authors found that neurons in multiple regions in the frontal and parietal cortex tended to encode signals related to previously rewarded actions more reliably than unrewarded actions. In addition, signals for rewarded choices in the supplementary eye field were attenuated during the visual search task and were correlated with the tendency to switch choices during the matching-pennies task. These results suggest that the supplementary eye field might play a unique role in encouraging animals to explore alternative decision-making strategies.

Repeated Cocaine Weakens GABAB-Girk Signaling in Layer 5/6 Pyramidal Neurons in the Prelimbic Cortex. Hearing M, Kotecki L, Marron Fernandez de Velasco E, Fajardo-Serrano A, Chung HJ, Lujan R, Wickman K. Neuron 2013; 80(1): 159-170.
Repeated cocaine exposure triggers adaptations in layer 5/6 glutamatergic neurons in the medial prefrontal cortex (mPFC) that promote behavioral sensitization and drug-seeking behavior. While suppression of metabotropic inhibitory signaling has been implicated in these behaviors, underlying mechanisms are unknown. Here, the authors show that Girk/K(IR)3 channels mediate most of the GABA(B) receptor (GABA(B)R)-dependent inhibition of layer 5/6 pyramidal neurons in the mPFC and that repeated cocaine suppresses this pathway. This adaptation was selective for GABA(B)R-dependent Girk signaling in layer 5/6 pyramidal neurons of the prelimbic cortex (PrLC) and involved a D1/5 dopamine receptor- and phosphorylation-dependent internalization of GABA(B)R and Girk channels. Persistent suppression of Girk signaling in layer 5/6 of the dorsal mPFC enhanced cocaine-induced locomotor activity and occluded behavioral sensitization. Thus, the cocaine-induced suppression of GABA(B)R-Girk signaling in layer 5/6 pyramidal neurons of the

prelimbic cortex appears to represent an early adaptation critical for promoting addiction-related behavior.

Fear Extinction Causes Target-Specific Remodeling Of Perisomatic Inhibitory Synapses. Trouche S, Sasaki JM, Tu T, Reijmers LG. Neuron 2013; 80(4): 1054-1065.
A more complete understanding of how fear extinction alters neuronal activity and connectivity within fear circuits may aid in the development of strategies to treat human fear disorders. Using a c-fos-based transgenic mouse, the authors found that contextual fear extinction silenced basal amygdala (BA) excitatory neurons that had been previously activated during fear conditioning. They hypothesized that the silencing of BA fear neurons was caused by an action of extinction on BA inhibitory synapses. In support of this hypothesis, they found extinction-induced target-specific remodeling of BA perisomatic inhibitory synapses originating from parvalbumin and cholecystokinin-positive interneurons. Interestingly, the predicted changes in the balance of perisomatic inhibition matched the silent and active states of the target BA fear neurons. These observations suggest that target-specific changes in perisomatic inhibitory synapses represent a mechanism through which experience can sculpt the activation patterns within a neural circuit.

Laminar and Columnar Development Of Barrel Cortex Relies On Thalamocortical Neurotransmission. Li H, Fertuzinhos S, Mohns E, Hnasko TS, Verhage M, Edwards R, Sestan N, Crair MC. Neuron 2013; 79(5): 970-986.
A dynamic interplay between intrinsic regional molecular cues and extrinsic factors from the thalamus shape multiple features of early cortical development. It remains uncertain and controversial, however, whether the initial formation of cortical columns depends on neuronal activity, and there is little evidence that cortical lamination or neuronal differentiation is influenced by extrinsic activity. The authors examined the role of thalamic-derived factors in cortical development by selectively eliminating glutamatergic synaptic transmission from thalamocortical neurons in mice and found that eliminating thalamocortical neurotransmission prevented the formation of "barrel" columns in somatosensory cortex. Interestingly, based on cytoarchitectonic criteria and genetic markers, blocking thalamocortical neurotransmission also perturbed the development of superficial cortical lamina and the morphologic development of neurons. These experiments demonstrate that barrels and aspects of the layer-dependent pattern of cortical cytoarchitecture, gene expression, and neuronal differentiation depend on thalamocortical neurotransmission, extending the apparent influence of extrinsic, presumably activity-dependent factors, on cortical development.

Nicotine Decreases Ethanol-Induced Dopamine Signaling and Increases Self-Administration Via Stress Hormones. Doyon WM, Dong Y, Ostroumov A, Thomas AM, Zhang TA, Dani JA. Neuron 2013; 79(3): 530-540.
Tobacco smoking is a well-known risk factor for subsequent alcohol abuse, but the neural events underlying this risk remain largely unknown. Alcohol and nicotine reinforcement involve common neural circuitry, including the mesolimbic dopamine system. The authors demonstrate in rodents that pre-exposure to nicotine increases alcohol self-administration and decreases alcohol-induced dopamine responses. The blunted dopamine response was due to increased inhibitory synaptic transmission onto dopamine neurons. Blocking stress hormone receptors prior to nicotine exposure prevented all interactions with alcohol that we measured, including the increased inhibition onto dopamine neurons, the decreased dopamine responses, and the increased alcohol self-administration. These results indicate that nicotine recruits neuroendocrine systems to influence neurotransmission and behavior associated with alcohol reinforcement.

Experience-Induced Arc/Arg3.1 Primes CA1 Pyramidal Neurons For Metabotropic Glutamate Receptor-Dependent Long-Term Synaptic Depression. Jakkamsetti V, Tsai NP, Gross C, Molinaro G, Collins KA, Nicoletti F, Wang KH, Osten P, Bassell GJ, Gibson JR, Huber KM. Neuron 2013; 80(1): 72-79.
A novel experience induces the Arc/Arg3.1 gene as well as plasticity of CA1 neural networks. To understand how these are linked, the authors briefly exposed GFP reporter mice of Arc transcription to a novel environment. Excitatory synaptic function of CA1 neurons with recent in vivo Arc induction (ArcGFP+) was similar to neighboring noninduced neurons. However, in response to group 1 metabotropic glutamate receptor (mGluR) activation, ArcGFP+ neurons preferentially displayed long-term synaptic depression (mGluR-LTD) and robust increases in dendritic Arc protein. mGluR-LTD in ArcGFP+ neurons required rapid protein synthesis and Arc, suggesting that dendritic translation of Arc underlies the priming of mGluR-LTD. In support of this idea, novelty exposure increased Arc messenger RNA in CA1 dendrites and promoted mGluR-induced translation of Arc in hippocampal synaptoneurosomes. Repeated experience suppressed synaptic transmission onto ArcGFP+ neurons and occluded mGluR-LTD ex vivo. mGluR-LTD priming in neurons with similar Arc activation history may contribute to encoding a novel environment.

Functional DNA Methylation Differences Between Tissues, Cell Types, and Across Individuals Discovered Using the M&M Algorithm. Zhang B, Zhou Y, Lin N, Lowdon RF, Hong C, Nagarajan RP, Cheng JB, Li D, Stevens M, Lee HJ, Xing X, Zhou J, Sundaram V, Elliott G, Gu J, Shi T, Gascard P, Sigaroudinia M, Tlsty TD, Kadlecek T, Weiss A, O'Geen H, Farnham PJ, Maire CL, Ligon KL, Madden PAF, Tam A, Moore R, Hirst M, Marra MA, Zhang B, Costello JF, Wang T. Genome Res 2013; 23(9): 1522-1540.
DNA methylation plays key roles in diverse biological processes such as X chromosome inactivation, transposable element repression, genomic imprinting, and tissue-specific gene expression. Sequencing-based DNA methylation profiling provides an unprecedented opportunity to map and compare complete DNA methylomes. This includes one of the most widely applied technologies for measuring DNA methylation: methylated DNA immunoprecipitation followed by sequencing (MeDIP-seq), coupled with a complementary method, methylation-sensitive restriction enzyme sequencing (MRE-seq). A computational approach that integrates data from these two different but complementary assays and predicts methylation differences between samples has been unavailable. Here, the authors present a novel integrative statistical framework M&M (for integration of MeDIP-seq and MRE-seq) that dynamically scales, normalizes, and combines MeDIP-seq and MRE-seq data to detect differentially methylated regions. Using sample-matched whole-genome bisulfite sequencing (WGBS) as a gold standard, the authors demonstrate superior accuracy and reproducibility of M&M compared to existing analytical methods for MeDIP-seq data alone. M&M leverages the complementary nature of MeDIP-seq and MRE-seq data to allow rapid comparative analysis between whole methylomes at a fraction of the cost of WGBS. Comprehensive analysis of nineteen human DNA methylomes with M&M reveals distinct DNA methylation patterns among different tissue types, cell types, and individuals, potentially underscoring divergent epigenetic regulation at different scales of phenotypic diversity. They find that differential DNA methylation at enhancer elements, with concurrent changes in histone modifications and transcription factor binding, is common at the cell, tissue, and individual levels, whereas promoter methylation is more prominent in reinforcing fundamental tissue identities.

HIV Infection Reveals Widespread Expansion Of Novel Centromeric Human Endogenous Retroviruses. Contreras-Galindo R, Kaplan MH, He S, Contreras-Galindo AC, Gonzalez-Hernandez MJ, Kappes F, Dube D, Chan SM, Robinson D, Meng F, Dai M, Gitlin SD, Chinnaiyan AM, Omenn GS, Markovitz DM. Genome Res 2013; 23(9): 1505-1513.
Human endogenous retroviruses (HERVs) make up 8% of the human genome. The HERV-K (HML-2) family is the most recent group of these viruses to have inserted into the genome, and the authors have detected the activation of HERV-K (HML-2) proviruses in the blood of patients with HIV-1 infection. They report that HIV-1 infection activates expression of a novel HERV-K (HML-2) provirus, termed K111, present in multiple copies in the centromeres of chromosomes throughout the human genome yet not annotated in the most recent human genome assembly. Infection with HIV-1 or stimulation with the HIV-1 Tat protein leads to the activation of K111 proviruses. K111 is present as a single copy in the genome of the chimpanzee, yet K111 is not found in the genomes of other primates. Remarkably, K111 proviruses appear in the genomes of the extinct Neanderthal and Denisovan, while modern humans have at least 100 K111 proviruses spread across the centromeres of 15 chromosomes. These studies suggest that the progenitor K111 integrated before the Homo-Pan divergence and expanded in copy number during the evolution of hominins, perhaps by recombination. The expansion of K111 provides sequence evidence suggesting that recombination between the centromeres of various chromosomes took place during the evolution of humans. K111 proviruses show significant sequence variations in each individual centromere, which may serve as markers in future efforts to annotate human centromere sequences. Further, this work is an example of the potential to discover previously unknown genomic sequences through the analysis of nucleic acids found in the blood of patients.

New Insights Into the Therapeutic Potential Of Girk Channels. Lujan R, Marron Fernandez de Velasco E, Aguado C, Wickman K. Trends Neurosci 2013.
G protein-dependent signaling pathways control the activity of excitable cells of the nervous system and heart, and are the targets of neurotransmitters, clinically relevant drugs, and drugs of abuse. G protein-gated inwardly rectifying potassium (K^+) (Girk/Kir3) channels are a key effector in inhibitory signaling pathways. Girk-dependent signaling contributes to nociception and analgesia, reward-related behavior, mood, cognition, and heart-rate regulation, and has been linked to epilepsy, Down syndrome, addiction, and arrhythmias. The authors discuss recent advances in our understanding of Girk channel structure, organization in signaling complexes, and plasticity, as well as progress on the development of subunit-selective Girk modulators. These findings offer new hope for the selective manipulation of Girk channels to treat a variety of debilitating afflictions.

Increasing Dopamine D2 Receptor Expression In the Adult Nucleus Accumbens Enhances Motivation. Trifilieff P, Feng B, Urizar E, Winiger V, Ward RD, Taylor KM, Martinez D, Moore H, Balsam PD, Simpson EH, Javitch JA. Mol Psychiatry 2013; 18(9): 1025-1033.
A decrease in dopamine D2 receptor (D2R) binding in the striatum is one of the most common findings in disorders that involve a dysregulation of motivation, including obesity, addiction and attention deficit hyperactivity disorder. As disruption of D2R signaling in the ventral striatum--including the nucleus accumbens (NAc)--impairs motivation, the authors sought to determine whether potentiating postsynaptic D2R-dependent signaling in the NAc would improve motivation. In this study, they used a viral vector strategy to overexpress postsynaptic D2Rs in either the NAc or the dorsal striatum. They investigated the effects of D2R overexpression on instrumental learning, willingness to work, use of reward value representations and modulation of motivation by reward associated cues. Overexpression of postsynaptic D2R in the NAc selectively increased motivation without altering consummatory behavior, the representation of the value of the

reinforcer, or the capacity to use reward associated cues in flexible ways. In contrast, D2R overexpression in the dorsal striatum did not alter performance on any of the tasks. Thus, consistent with numerous studies showing that reduced D2R signaling impairs motivated behavior, these data show that postsynaptic D2R overexpression in the NAc specifically increases an animal's willingness to expend effort to obtain a goal. Taken together, these results provide insight into the potential impact of future therapeutic strategies that enhance D2R signaling in the NAc.

Genome-Wide Association Study Of Cocaine Dependence and Related Traits: FAM53B Identified As A Risk Gene. Gelernter J, Sherva R, Koesterer R, Almasy L, Zhao H, Kranzler HR, Farrer L. Mol Psychiatry 2013.
The authors report a genome-wide association study (GWAS) for cocaine dependence (CD) in three sets of African- and European-American subjects (AAs and EAs, respectively) to identify pathways, genes and alleles important in CD risk. The discovery GWAS data set (n=5697 subjects) was genotyped using the Illumina OmniQuad microarray (8,90,000 analyzed single-nucleotide polymorphisms (SNPs)). Additional genotypes were imputed based on the 1000 Genomes reference panel. Top-ranked findings were evaluated by incorporating information from publicly available GWAS data from 4063 subjects. Then, the most significant GWAS SNPs were genotyped in 2549 independent subjects. The authors observed one genome-wide-significant (GWS) result: rs2629540 at the FAM53B ('family with sequence similarity 53, member B') locus. This was supported in both AAs and EAs; P-value (meta-analysis of all samples)=4.28×10^{-8}. The gene maps to the same chromosomal region as the maximum peak the authors observed in a previous linkage study. NCOR2 (nuclear receptor corepressor 2) SNP rs150954431 was associated with P=1.19×10^{-9} in the EA discovery sample. SNP rs2456778, which maps to CDK1 ('cyclin-dependent kinase 1'), was associated with cocaine-induced paranoia in AAs in the discovery sample only (P=4.68×10^{-8}). This is the first study to identify risk variants for CD using GWAS. Our results implicate novel risk loci and provide insights into potential therapeutic and prevention strategies.

Evidence For the Role Of EPHX2 Gene Variants In Anorexia Nervosa. Scott-Van Zeeland AA, Bloss CS, Tewhey R, Bansal V, Torkamani A, Libiger O, Duvvuri V, Wineinger N, Galvez L, Darst BF, Smith EN, Carson A, Pham P, Phillips T, Villarasa N, Tisch R, Zhang G, Levy S, Murray S, Chen W, Srinivasan S, Berenson G, Brandt H, Crawford S, Crow S, Fichter MM, Halmi KA, Johnson C, Kaplan AS, La Via M, Mitchell JE, Strober M, Rotondo A, Treasure J, Woodside DB, Bulik CM, Keel P, Klump KL, Lilenfeld L, Plotnicov K, Topol EJ, Shih PB, Magistretti P, Bergen AW, Berrettini W, Kaye W, Schork NJ. Mol Psychiatry 2013.
Anorexia nervosa (AN) and related eating disorders are complex, multifactorial neuropsychiatric conditions with likely rare and common genetic and environmental determinants. To identify genetic variants associated with AN, the authors pursued a series of sequencing and genotyping studies focusing on the coding regions and upstream sequence of 152 candidate genes in a total of 1205 AN cases and 1948 controls. They identified individual variant associations in the Estrogen Receptor-ß (ESR2) gene, as well as a set of rare and common variants in the Epoxide Hydrolase 2 (EPHX2) gene, in an initial sequencing study of 261 early-onset severe AN cases and 73 controls (P=0.0004). The association of EPHX2 variants was further delineated in: (1) a pooling-based replication study involving an additional 500 AN patients and 500 controls (replication set P=0.00000016); (2) single-locus studies in a cohort of 386 previously genotyped broadly defined AN cases and 295 female population controls from the Bogalusa Heart Study (BHS) and a cohort of 58 individuals with self-reported eating disturbances and 851 controls (combined smallest single locus P<0.01). As EPHX2 is known to influence cholesterol metabolism, and AN is often associated with elevated cholesterol levels, the authors also investigated the association of EPHX2 variants and

longitudinal body mass index (BMI) and cholesterol in BHS female and male subjects (N=229) and found evidence for a modifying effect of a subset of variants on the relationship between cholesterol and BMI ($P<0.01$). These findings suggest a novel association of gene variants within EPHX2 to susceptibility to AN and provide a foundation for future study of this important yet poorly understood condition.

Evidence From Mouse and Man For A Role Of Neuregulin 3 In Nicotine Dependence. Turner JR, Ray R, Lee B, Everett L, Xiang J, Jepson C, Kaestner KH, Lerman C, Blendy JA. Mol Psychiatry 2013.
Addiction to nicotine and the ability to quit smoking are influenced by genetic factors. The authors used functional genomic approaches (chromatin immunoprecipitation (ChIP) and whole-genome sequencing) to identify cAMP response element-binding protein (CREB) targets following chronic nicotine administration and withdrawal (WD) in rodents. They found that chronic nicotine and WD differentially modulate CREB binding to the gene for neuregulin 3 (NRG3). Quantitative analysis of saline, nicotine and nicotine WD in two biological replicates corroborate this finding, with NRG3 increases in both mRNA and protein following WD from chronic nicotine treatment. To translate these data for human relevance, single-nucleotide polymorphisms (SNPs) across NRG3 were examined for association with prospective smoking cessation among smokers of European ancestry treated with transdermal nicotine in two independent cohorts. Individual SNP and haplotype analysis support the association of NRG3 SNPs and smoking cessation success. NRG3 is a neural-enriched member of the epidermal growth factor family, and a specific ligand for the receptor tyrosine kinase ErbB4, which is also upregulated following nicotine treatment and WD. Mice with significantly reduced levels of NRG3 or pharmacological inhibition of ErbB4 show similar reductions in anxiety following nicotine WD compared with control animals, suggesting a role for NRG3 in nicotine dependence. Although the function of the SNP in NRG3 in humans is not known, these data suggest that Nrg3/ErbB4 signaling may be an important factor in nicotine dependence.

Human Cytomegalovirus Tegument Protein Pul83 Inhibits IFI16-Mediated DNA Sensing For Immune Evasion. Li T, Chen J, Cristea IM. Cell Host Microbe 2013; 14(5): 591-599.
Nuclear sensing of viral DNA has emerged as an essential step in innate immune responses against herpes viruses. Here, the authors provide mechanistic insight into host recognition of human cytomegalovirus (HCMV) and subsequent immune evasion by this prominent DNA virus. They establish that the interferon-inducible protein IFI16 acts as a nuclear DNA sensor following HCMV infection, binding viral DNA and triggering expression of antiviral cytokines via the STING-TBK1-IRF3 signaling pathway. The HCMV tegument protein pUL83 inhibits this response by interacting with the IFI16 pyrin domain, blocking its oligomerization upon DNA sensing and subsequent immune signals. pUL83 disrupts IFI16 by concerted action of its N- and C-terminal domains, in which an evolutionarily conserved N-terminal pyrin association domain (PAD) binds IFI16. Additionally, phosphorylation of the N-terminal domain modulates pUL83-mediated inhibition of pyrin aggregation. Collectively, these data elucidate the interplay between host DNA sensing and HCMV immune evasion, providing targets for restoring antiviral immunity.

Chronic THC Intake Modifies Fundamental Cerebellar Functions. Stella N. J Clin Invest 2013; 123(8): 3208-3210.
Delta9-tetrahydrocannabinol (THC), the principal bioactive component in the Cannabis plant, is truly a captivating drug. Acute and chronic THC intake produces a spectrum of biological effects ranging from transient psychotropic effects to prolonged medicinal benefits, many of which have been fostered for centuries by our society. In the July 2013 issue of the JCI, Cutando et al.

combined mouse genetics with classic mouse behavioral analysis to deepen our understanding of the physiological consequence of subchronic THC intake on eyeblink reflexes, a fundamental neuronal adaptive response, revealing that this regimen leads to downregulation of the cannabinoid CB1 receptor (referred to as CB1 in the Cutando et al. article) in cerebellar stress fibers and the activation of microglia, raising provocative new questions about the safety profile of regimented THC intake.

Combinatory Approaches Prevent Preterm Birth Profoundly Exacerbated By Gene-Environment Interactions. Cha J, Bartos A, Egashira M, Haraguchi H, Saito-Fujita T, Leishman E, Bradshaw H, Dey SK, Hirota Y. J Clin Invest 2013; 123(9): 4063-4075.
There are currently more than 15 million preterm births each year. The authors propose that gene-environment interaction is a major contributor to preterm birth. To address this experimentally, they generated a mouse model with uterine deletion of Trp53, which exhibits approximately 50% incidence of spontaneous preterm birth due to premature decidual senescence with increased mTORC1 activity and COX2 signaling. Here they provide evidence that this predisposition provoked preterm birth in 100% of females exposed to a mild inflammatory insult with LPS, revealing the high significance of gene-environment interactions in preterm birth. More intriguingly, preterm birth was rescued in LPS-treated Trp53-deficient mice when they were treated with a combination of rapamycin (mTORC1 inhibitor) and progesterone (P4), without adverse effects on maternal or fetal health. These results provide evidence for the cooperative contributions of two sites of action (decidua and ovary) toward preterm birth. Moreover, a similar signature of decidual senescence with increased mTORC1 and COX2 signaling was observed in women undergoing preterm birth. Collectively, these findings show that superimposition of inflammation on genetic predisposition results in high incidence of preterm birth and suggest that combined treatment with low doses of rapamycin and P4 may help reduce the incidence of preterm birth in high-risk women.

Impaired Periamygdaloid-Cortex Prodynorphin Is Characteristic Of Opiate Addiction and Depression. Anderson SAR, Michaelides M, Zarnegar P, Ren Y, Fagergren P, Thanos PK, Wang GJ, Bannon M, Neumaier JF, Keller E, Volkow ND, Hurd YL. J Clin Invest 2013.
Negative affect is critical for conferring vulnerability to opiate addiction as reflected by the high comorbidity of opiate abuse with major depressive disorder (MDD). Rodent models implicate amygdala prodynorphin (Pdyn) as a mediator of negative affect; however, evidence of PDYN involvement in human negative affect is limited. Here, the authors found reduced PDYN mRNA expression in the postmortem human amygdala nucleus of the periamygdaloid cortex (PAC) in both heroin abusers and MDD subjects. Similar to humans, rats that chronically self-administered heroin had reduced Pdyn mRNA expression in the PAC at a time point associated with a negative affective state. Using the in vivo functional imaging technology DREAMM (DREADD-assisted metabolic mapping, where DREADD indicates designer receptors exclusively activated by designer drugs), they found that selective inhibition of Pdyn-expressing neurons in the rat PAC increased metabolic activity in the extended amygdala, which is a key substrate of the extrahypothalamic brain stress system. In parallel, PAC-specific Pdyn inhibition provoked negative affect-related physiological and behavioral changes. Altogether, this translational study supports a functional role for impaired Pdyn in the PAC in opiate abuse through activation of the stress and negative affect neurocircuitry implicated in addiction vulnerability.

Whole-Brain Circuit Dissection In Free-Moving Animals Reveals Cell-Specific Mesocorticolimbic Networks. Michaelides M, Anderson SAR, Ananth M, Smirnov D, Thanos PK, Neumaier JF, Wang GJ, Volkow ND, Hurd YL. J Clin Invest 2013.
The ability to map the functional connectivity of discrete cell types in the intact mammalian brain during behavior is crucial for advancing our understanding of brain function in normal and disease states. The authors combined designer receptor exclusively activated by designer drug (DREADD) technology and behavioral imaging with μPET and [18F]fluorodeoxyglucose (FDG) to generate whole-brain metabolic maps of cell-specific functional circuits during the awake, freely moving state. The authors have termed this approach DREADD-assisted metabolic mapping (DREAMM) and documented its ability in rats to map whole-brain functional anatomy. They applied this strategy to evaluating changes in the brain associated with inhibition of prodynorphin-expressing (Pdyn-expressing) and of proenkephalin-expressing (Penk-expressing) medium spiny neurons (MSNs) of the nucleus accumbens shell (NAcSh), which have been implicated in neuropsychiatric disorders. DREAMM revealed discrete behavioral manifestations and concurrent engagement of distinct corticolimbic networks associated with dysregulation of Pdyn and Penk in MSNs of the NAcSh. Furthermore, distinct neuronal networks were recruited in awake versus anesthetized conditions. These data demonstrate that DREAMM is a highly sensitive, molecular, high-resolution quantitative imaging approach.

Determination Of Genotype Combinations That Can Predict The Outcome Of the Treatment Of Alcohol Dependence Using The 5-HT(3) Antagonist Ondansetron. Johnson BA, Seneviratne C, Wang XQ, Ait-Daoud N, Li MD. Am J Psychiatry 2013; 170(9): 1020-1031.
The authors previously reported that the 5'-HTTLPR-LL and rs1042173-TT (SLC6A4-LL/TT) genotypes in the serotonin transporter gene predicted a significant reduction in the severity of alcohol consumption among alcoholics receiving the 5-HT3 antagonist ondansetron. In this study, they explored additional markers of ondansetron treatment response in alcoholics by examining polymorphisms in the HTR3A and HTR3B genes, which regulate directly the function and binding of 5-HT3 receptors to ondansetron. The authors genotyped one rare and 18 common single-nucleotide polymorphisms in HTR3A and HTR3B in the same sample that they genotyped for SLC6A4-LL/TT in the previous randomized, double-blind, 11-week clinical trial. Participants were 283 European Americans who received oral ondansetron (4 mg/kg of body weight twice daily) or placebo along with weekly cognitive-behavioral therapy. Associations of individual and combined genotypes with treatment response on drinking outcomes were analyzed. Individuals carrying one or more of genotypes rs1150226-AG and rs1176713-GG in HTR3A and rs17614942-AC in HTR3B showed a significant overall mean difference between ondansetron and placebo in drinks per drinking day (22.50; effect size=0.867), percentage of heavy drinking days (220.58%; effect size=0.780), and percentage of days abstinent (18.18%; effect size=0.683). Combining these HTR3A/HTR3B and SLC6A4-LL/TT genotypes increased the target cohort from approaching 20% (identified in the previous study) to 34%. The authors present initial evidence suggesting that a combined fivemarker genotype panel can be used to predict the outcome of treatment of alcohol dependence with ondansetron. Additional, larger pharmacogenetic studies would help to validate these results.

Stochastic Gene Expression In Mammals: Lessons From Olfaction. Magklara A, Lomvardas S. Trends Cell Biol 2013; 23(9): 449-456.
One of the remarkable characteristics of higher organisms is the enormous assortment of cell types that emerge from a common genome. The immune system, with the daunting duty of detecting an astounding number of pathogens, and the nervous system with the equally bewildering task of

perceiving and interpreting the external world, are the quintessence of cellular diversity. As we began to appreciate decades ago, achieving distinct expression programs among similar cell types cannot be accomplished solely by deterministic regulatory systems, but by the involvement of some type of stochasticity. In the last few years our understanding of these non-deterministic mechanisms is advancing, and this review will provide a brief summary of the current view of stochastic gene expression with focus on olfactory receptor (OR) gene choice, the epigenetic underpinnings of which recently began to emerge.

Mechanisms Of Dopamine Transporter Regulation In Normal and Disease States. Vaughan RA, Foster JD Trends Pharmacol Sci 2013; 34(9): 489-496.
The dopamine (DA) transporter (DAT) controls the spatial and temporal dynamics of DA neurotransmission by driving reuptake of extracellular transmitter into presynaptic neurons. Many diseases such as depression, bipolar disorder, Parkinson's disease (PD), and attention deficit hyperactivity disorder (ADHD) are associated with abnormal DA levels, implicating DAT as a factor in their etiology. Medications used to treat these disorders and many addictive drugs target DAT and enhance dopaminergic signaling by suppressing transmitter reuptake. We now understand that the transport and binding properties of DAT are regulated by complex and overlapping mechanisms that provide neurons with the ability to modulate DA clearance in response to physiological demands. These processes are controlled by endogenous signaling pathways and affected by exogenous transporter ligands, demonstrating their importance for normal neurotransmission, drug abuse, and disease treatments. Increasing evidence supports the disruption of these mechanisms in DA disorders, implicating dysregulation of transport in disease etiologies and suggesting these processes as potential points for therapeutic manipulation of DA availability.

The Membrane Protein Leut In Micellar Systems: Aggregation Dynamics and Detergent Binding To the S2 Site. Khelashvili G, LeVine MV, Shi L, Quick M, Javitch JA, Weinstein H. J Am Chem Soc 2013; 135(38): 14266-14275.
Structural and functional properties of integral membrane proteins are often studied in detergent micellar environments (proteomicelles), but how such proteomicelles form and organize is not well understood. This makes it difficult to evaluate the relationship between the properties of the proteins measured in such a detergent-solubilized form and under native conditions. To obtain mechanistic information about this relationship for the leucine transporter (LeuT), a prokaryotic homologue of the mammalian neurotransmitter/sodium symporters (NSSs), the authors studied the properties of proteomicelles formed by n-dodecyl-β,D-maltopyranoside (DDM) detergent. Extensive atomistic molecular dynamics simulations of different protein/detergent/water number ratios revealed the formation of a proteomicelle characterized by a constant-sized shell of detergents surrounding LeuT protecting its transmembrane segments from unfavorable hydrophobic/hydrophilic exposure. Regardless of the DDM content in the simulated system, this shell consisted of a constant number of DDM molecules (~120 measured at a 4 Å cutoff distance from LeuT). In contrast, the overall number of DDMs in the proteomicelle (aggregation number) was found to depend on the detergent concentration, reaching a saturation value of 226±17 DDMs in the highest concentration regime simulated. Remarkably, the authors found that at high detergent-to-protein ratios they observed two independent ways of DDM penetration into LeuT, both leading to a positioning of the DDM molecule in the second substrate (S2) binding site of LeuT. Consonant with several recent experimental studies demonstrating changes in functional properties of membrane proteins due to detergent, these findings highlight how the environment in which the membrane proteins are examined may affect the outcome and interpretation of their mechanistic features.

Spectral Evolution Of A Photochemical Protecting Group For Orthogonal Two-Color Uncaging With Visible Light. Olson JP, Banghart MR, Sabatini BL, Ellis-Davies GCR. J Am Chem Soc 2013; 135(42): 15948-15954.
Caged compounds are molecules rendered functionally inert by derivatization with a photochemical protecting group. The authors describe the design logic behind the development of a diethylaminocoumarin (DEAC) caging chromophore, DEAC450, that absorbs blue light strongly (ε450 = 43,000 M(-1) cm(-1)) and violet light 11-fold more weakly. The absorption minimum is in the wavelength range (340-360 nm) that is traditionally used for photolysis of many widely used nitroaromatic caged compounds (e.g., 4-carboxymethoxy-5,7-dinitroindolinyl(CDNI)-GABA). The authors used this chromophore to synthesize DEAC450-caged cAMP and found this probe was very stable toward aqueous hydrolysis in the electronic ground state but was photolyzed with a quantum efficiency of 0.78. When DEAC450-cAMP and CDNI-GABA where co-applied to striatal cholinergic interneurons, the caged compounds were photolyzed in an chromatically orthogonal manner using blue and violet light so as to modulate the neuronal firing rate in a bidirectional way.

Hepatic Stellate Cells, Liver Innate Immunity, and Hepatitis C Virus. Wang Y, Li J, Wang X, Sang M, Ho W. J Gastroenterol Hepatol 2013; 28 Suppl 1: 112-115.
Chronic hepatitis C virus (HCV) infection can cause liver damage, ranging from mild to more severe conditions, such as fibrosis and cirrhosis. Hepatic stellate cell (HSC) activation is a key event in HCV-induced liver fibrosis. HSCs express several HCV coreceptors that interact with HCV proteins, promoting liver fibrogenesis. In addition, HSCs have the ability to engulf apoptotic bodies of hepatocytes induced by HCV and trigger a profibrogenic response. Recent studies have suggested that HSCs may play a novel role in the liver innate immunity. HSCs enhanced differentiation and accumulation of regulatory T cells. HSCs-activated natural killer cells could produce γ-interferon that inhibits HCV replication. Importantly, HSCs possess functional Toll-like receptor-3 and retinoic acid-inducible gene I that can be activated by their ligands (poly I :C,5'ppp-dsRNA), leading to the induction of interferon and inhibition of HCV replication in hepatocytes. These new observations highlight the importance of HSCs in liver immunity against HCV, which is the focus of this review paper.

GPR171 Is A Hypothalamic G Protein-Coupled Receptor For Biglen, A Neuropeptide Involved In Feeding. Gomes I, Aryal DK, Wardman JH, Gupta A, Gagnidze K, Rodriguiz RM, Kumar S, Wetsel WC, Pintar JE, Fricker LD, Devi LA. Proc Natl Acad Sci U S A 2013; 110(40): 16211-16216.
Multiple peptide systems, including neuropeptide Y, leptin, ghrelin, and others, are involved with the control of food intake and body weight. The peptide LENSSPQAPARRLLPP (BigLEN) has been proposed to act through an unknown receptor to regulate body weight. In the present study, the authors used a combination of ligand-binding and receptor-activity assays to characterize a Gαi/o protein-coupled receptor activated by BigLEN in the mouse hypothalamus and Neuro2A cells. They then selected orphan G protein-coupled receptors expressed in the hypothalamus and Neuro2A cells and tested each for activation by BigLEN. G protein-coupled receptor 171 (GPR171) is activated by BigLEN, but not by the C terminally truncated peptide LittleLEN. The four C-terminal amino acids of BigLEN are sufficient to bind and activate GPR171. Overexpression of GPR171 leads to an increase, and knockdown leads to a decrease, in binding and signaling by BigLEN and the C-terminal peptide. In the hypothalamus GPR171 expression complements the expression of BigLEN, and its level and activity are elevated in mice lacking BigLEN. In mice, shRNA-mediated knockdown of hypothalamic GPR171 leads to a decrease in BigLEN signaling and results in changes in food intake and metabolism. The combination of GPR171 shRNA together with

neutralization of BigLEN peptide by antibody absorption nearly eliminates acute feeding in food-deprived mice. Taken together, these results demonstrate that GPR171 is the BigLEN receptor and that the BigLEN-GPR171 system plays an important role in regulating responses associated with feeding and metabolism in mice.

Bispecific Antibodies Directed To CD4 Domain 2 and HIV Envelope Exhibit Exceptional Breadth and Picomolar Potency Against HIV-1. Pace CS, Song R, Ochsenbauer C, Andrews CD, Franco D, Yu J, Oren DA, Seaman MS, Ho DD. Proc Natl Acad Sci U S A 2013; 110(33): 13540-13545.
In the absence of an effective HIV-1 vaccine, passive immunization using broadly neutralizing Abs or Ab-like molecules could provide an alternative to the daily administration of oral antiretroviral agents that has recently shown promise as preexposure prophylaxis. Currently, no single broadly neutralizing Ab (bNAb) or combination of bNAbs neutralizes all HIV-1 strains at practically achievable concentrations in vivo. To address this problem, the authors created bispecific Abs that combine the HIV-1 inhibitory activity of ibalizumab (iMab), a humanized mAb directed to domain 2 of human CD4, with that of anti-gp120 bNAbs. These bispecific bNAbs (BibNAbs) exploit iMab's potent anti-HIV-1 activity and demonstrated clinical efficacy and safety to anchor and thereby concentrate a second broadly neutralizing agent at the site of viral entry. Two BibNabs, PG9-iMab and PG16-iMab, exhibit exceptional breadth and potency, neutralizing 100% of the 118 viruses tested at low picomolar concentrations, including viruses resistant to both parental mAbs. The enhanced potency of these BibNAbs was entirely dependent on CD4 anchoring, not on membrane anchoring per se, and required optimal Ab geometry and linker length. The authors propose that iMab-based BibNAbs, such as PG9-iMab and PG16-iMab, are promising candidates for passive immunization to prevent HIV-1 infection.

AMPA Receptor Phluorin-Glua2 Reports NMDA Receptor-Induced Intracellular Acidification In Hippocampal Neurons. Rathje M, Fang H, Bachman JL, Anggono V, Gether U, Huganir RL, Madsen KL. Proc Natl Acad Sci U S A 2013; 110(35): 14426-14431.
NMDA receptor activation promotes endocytosis of AMPA receptors, which is an important mechanism underlying long-term synaptic depression. The pH-sensitive GFP variant pHluorin fused to the N terminus of GluA2 (pH-GluA2) has been used to assay NMDA-mediated AMPA receptor endocytosis and recycling. Here, the authors demonstrate that in somatic and dendritic regions of hippocampal neurons a large fraction of the fluorescent signal originates from intracellular pH-GluA2, and that the decline in fluorescence in response to NMDA and AMPA primarily describes an intracellular acidification, which quenches the pHluorin signal from intracellular receptor pools. Neurons expressing an endoplasmic reticulum-retained mutant of GluA2 (pH-GluA2 ΔC49) displayed a larger response to NMDA than neurons expressing wild-type pH-GluA2. A similar NMDA-elicited decline in pHluorin signal was observed by expressing cytosolic pHluorin alone without fusion to GluA2 (cyto-pHluorin). Intracellular acidification in response to NMDA was further confirmed by using the ratiometric pH indicator carboxy-SNARF-1. The NMDA-induced decline was followed by rapid recovery of the fluorescent signal from both cyto-pHluorin and pH-GluA2. The recovery was sodium-dependent and sensitive to Na(+)/H(+)-exchanger (NHE) inhibitors. Moreover, recovery was more rapid after shRNA-mediated knockdown of the GluA2 binding PDZ domain-containing protein interacting with C kinase 1 (PICK1). Interestingly, the accelerating effect of PICK1 knockdown on the fluorescence recovery was eliminated in the presence of the NHE1 inhibitor zoniporide. These results indicate that the pH-GluA2 recycling assay is an unreliable assay for studying AMPA receptor trafficking and also suggest a role for PICK1 in regulating intracellular pH via modulation of NHE activity.

Disruption Of the Expression Of the Proprotein Convertase PC7 Reduces BDNF Production and Affects Learning and Memory In Mice. Wetsel WC, Rodriguiz RM, Guillemot J, Rousselet E, Essalmani R, Kim IH, Bryant JC, Marcinkiewicz J, Desjardins R, Day R, Constam DB, Prat A, Seidah NG. Proc Natl Acad Sci U S A 2013; 110(43): 17362-17367.
PC7 belongs to the proprotein convertase family, whose members are implicated in the cleavage of secretory precursors. The in vivo function of PC7 is unknown. Herein, the authors find that the precursor proBDNF is processed into mature BDNF in COS-1 cells coexpressing proBDNF with either PC7 or Furin. Conversely, the processing of proBDNF into BDNF is markedly reduced in the absence of either Furin or PC7 in mouse primary hepatocytes. In vivo the authors observe that BDNF and PC7 mRNAs are colocalized in mouse hippocampus and amygdala and that mature BDNF protein levels are reduced in these brain areas in PC7 KO mice but not in the hippocampus of PC1/3 KO mice. Various behavioral tests reveal that in PC7 KO mice spatial memory is intact and plasticity of responding is mildly abnormal. Episodic and emotional memories are severely impaired, but both are rescued with the tyrosine receptor kinase B agonist 7,8-dihydroxyflavone. Altogether, these results support an in vivo role for PC7 in the regulation of certain types of cognitive performance, in part via proBDNF processing. Because polymorphic variants of human PC7 are being characterized, it will be important in future studies to determine their effects on additional physiological and behavioral processes.

Reprogramming Of G Protein-Coupled Receptor Recycling and Signaling By A Kinase Switch. Vistein R, Puthenveedu MA. Proc Natl Acad Sci U S A 2013; 110(38): 15289-15294.
The postendocytic recycling of signaling receptors is subject to multiple requirements. Why this is so, considering that many other proteins can recycle without apparent requirements, is a fundamental question. Here the authors show that cells can leverage these requirements to switch the recycling of the beta-2 adrenergic receptor (B2AR), a prototypic signaling receptor, between sequence-dependent and bulk recycling pathways, based on extracellular signals. This switch is determined by protein kinase A-mediated phosphorylation of B2AR on the cytoplasmic tail. The phosphorylation state of B2AR dictates its partitioning into spatially and functionally distinct endosomal microdomains mediating bulk and sequence-dependent recycling, and also regulates the rate of B2AR recycling and resensitization. These results demonstrate that G protein-coupled receptor recycling is not always restricted to the sequence-dependent pathway, but may be reprogrammed as needed by physiological signals. Such flexible reprogramming might provide a versatile method for rapidly modulating cellular responses to extracellular signaling.

Presynaptic Gating Of Excitation In tThe Dorsal Raphe Nucleus By GABA. Soiza-Reilly M, Anderson WB, Vaughan CW, Commons KG. Proc Natl Acad Sci U S A 2013; 110(39): 15800-15805.
The dorsal raphe nucleus (DR) controls forebrain serotonin neurotransmission to influence emotional states. GABA neurotransmission in the DR has been implicated in regulating sleep/wake states and influencing anxiety and aggression. To gain insight into how GABA regulates DR activity, the authors analyzed the organization of both GABA and glutamate axons in the rat DR using a high-resolution immunofluorescence technique, array tomography, as well as EM. This analysis revealed that a third or more of GABA-containing axons are organized in synaptic triads with a glutamatergic axon and a common postsynaptic target. Electrophysio-logical recordings showed that GABA has the capacity to presynaptically gate glutamate release in the DR through a combination of GABA-A and GABA-B receptor-mediated effects. Thus, GABA-glutamate synaptic triads are a common feature of the network architecture of the DR with the potential to regulate excitation of the nucleus.

NR2B Subunit Of the NMDA Glutamate Receptor Regulates Appetite In the Parabrachial Nucleus. Wu Q, Zheng R, Srisai D, McKnight GS, Palmiter RD. Proc Natl Acad Sci U S A 2013; 110(36): 14765-14770.
Diphtheria toxin-mediated, acute ablation of hypothalamic neurons expressing agouti-related protein (AgRP) in adult mice leads to anorexia and starvation within 7 d that is caused by hyperactivity of neurons within the parabrachial nucleus (PBN). Because NMDA glutamate receptors are involved in various synaptic plasticity-based behavioral modifications, the authors hypothesized that modulation of the NR2A and NR2B subunits of the NMDA receptor in PBN neurons could contribute to the anorexia phenotype. They observed by Western blot analyses that ablation of AgRP neurons results in enhanced expression of NR2B along with a modest suppression of NR2A. Interestingly, systemic administration of LiCl in a critical time window before AgRP neuron ablation abolished the anorectic response. LiCl treatment suppressed NR2B levels in the PBN and ameliorated the local Fos induction that is associated with anorexia. This protective role of LiCl on feeding was blunted in vagotomized mice. Chronic infusion of RO25-6981, a selective NR2B inhibitor, into the PBN recapitulated the role of LiCl in maintaining feeding after AgRP neuron ablation. The authors suggest that the accumulation of NR2B subunits in the PBN contributes to aphagia in response to AgRP neuron ablation and may be involved in other forms of anorexia.

Alteration Of Genic 5-Hydroxymethylcytosine Patterning In Olfactory Neurons Correlates With Changes In Gene Expression and Cell Identity. Colquitt BM, Allen WE, Barnea G, Lomvardas S. Proc Natl Acad Sci U S A 2013; 110(36): 14682-14687.
The modified DNA base 5-hydroxymethylcytosine (5hmC) is enriched in neurons where it may contribute to gene regulation and cellular identity. To determine how 5hmC influences gene expression in an in vivo neuronal population, the authors assessed the patterning and function of the base along the developmental lineage of the main olfactory epithelium-from multipotent stem cells through neuronal progenitors to mature olfactory sensory neurons (mOSNs). They find that 5hmC increases over gene bodies during mOSN development with substantial patterning occuring between the progenitor and mOSN stages. Although gene-body 5hmC levels correlate with gene expression in all three developmental cell types, this association is particularly pronounced within mOSNs. Overexpression of Tet3 in mOSNs markedly alters gene-body 5hmC levels and gene expression in a manner consistent with a positive role for 5hmC in transcription. Moreover, Tet3 overexpression disrupts olfactory receptor expression and the targeting of axons to the olfactory bulb, key molecular and anatomical features of the olfactory system. These results suggest a physiologically significant role for gene-body 5hmC in transcriptional facilitation and the maintenance of cellular identity independent of its function as an intermediate to demethylation.

Activation of GABAergic Neurons in the Interpeduncular Nucleus Triggers Physical Nicotine Withdrawal Symptoms. Zhao-Shea R, Liu L, Pang X, Gardner PD, Tapper AR. Curr Biol 2013.
Chronic exposure to nicotine elicits physical dependence in smokers, yet the mechanism and neuroanatomical bases for withdrawal symptoms are unclear. As in humans, rodents undergo physical withdrawal symptoms after cessation from chronic nicotine characterized by increased scratching, head nods, and body shakes. Here the authors show that induction of physical nicotine withdrawal symptoms activates GABAergic neurons within the interpeduncular nucleus (IPN). Optical activation of IPN GABAergic neurons via light stimulation of channelrhodopsin elicited physical withdrawal symptoms in both nicotine-naive and chronic-nicotine-exposed mice. Dampening excitability of GABAergic neurons during nicotine withdrawal through IPN-selective infusion of an NMDA receptor antagonist or through blockade of IPN neurotrans-mission from the

medial habenula reduced IPN neuronal activation and alleviated withdrawal symptoms. During chronic nicotine exposure, nicotinic acetylcholine receptors containing the β4 subunit were upregulated in somatostatin interneurons clustered in the dorsal region of the IPN. Blockade of these receptors induced withdrawal signs more dramatically in nicotine-dependent compared to nicotine-naive mice and activated nonsomatostatin neurons in the IPN. Together, these data indicate that therapeutic strategies to reduce IPN GABAergic neuron excitability during nicotine withdrawal, for example, by activating nicotinic receptors on somatostatin interneurons, may be beneficial for alleviating withdrawal symptoms and facilitating smoking cessation.

Quantitation Of Endogenous Peptides Using Mass Spectrometry Based Methods. Romanova EV, Dowd SE, Sweedler JV. Curr Opin Chem Biol 2013; 17(5): 801-808.
The mass spectrometry-based 'omics' sub-discipline that focuses on comprehensive, often exploratory, analyses of endogenous peptides involved in cell-to-cell communication is oftentimes referred to as peptidomics. Although the progress in bioanalytical technology development for peptide discovery has been tremendous, perhaps the largest advances have involved robust quantitative mass spectrometric approaches and data mining algorithms. These efforts have accelerated the discovery and validation of biomarkers, functionally important posttranslational modifications, and unexpected molecular interactions, information that aids drug development. In this article we outline the current approaches used in quantitative peptidomics and the technical challenges that stimulate new advances in the field, while also reviewing the newest literature on functional characterizations of endogenous peptides using quantitative mass spectrometry.

Exercise As A Novel Treatment For Drug Addiction: A Neurobiological and Stage-Dependent Hypothesis. Lynch WJ, Peterson AB, Sanchez V, Abel J, Smith MA. Neurosci Biobehav Rev (2013); 37(8): 1622-1644.
Physical activity, and specifically exercise, has been suggested as a potential treatment for drug addiction. In this review, the authors discuss clinical and preclinical evidence for the efficacy of exercise at different phases of the addiction process. Potential neurobiological mechanisms are also discussed focusing on interactions with dopaminergic and glutamatergic signaling and chromatin remodeling in the reward pathway. While exercise generally produces an efficacious response, certain exercise conditions may be either ineffective or lead to detrimental effects depending on the level/type/timing of exercise exposure, the stage of addiction, the drug involved, and the subject population. During drug use initiation and withdrawal, its efficacy may be related to its ability to facilitate dopaminergic transmission, and once addiction develops, its efficacy may be related to its ability to normalize glutamatergic and dopaminergic signaling and reverse drug-induced changes in chromatin via epigenetic interactions with brain-derived neurotrophic factor (BDNF) in the reward pathway. The authors conclude with future directions, including the development of exercise-based interventions alone or as an adjunct to other strategies for treating drug addiction.

Low Baseline CD4+ Count Is Associated With Greater Bone Mineral Density Loss After Antiretroviral Therapy Initiation. Grant PM, Kitch D, McComsey GA, Dube MP, Haubrich R, Huang J, Riddler S, Tebas P, Zolopa AR, Collier AC, Brown TT. Clin Infect Dis 2013; 57(10): 1483-1488.
Bone mineral density (BMD) decreases 2%-6% in the 2 years after antiretroviral therapy (ART) initiation. Pre-ART immune deficiency and early immune recovery may contribute to this loss. The authors pooled data from 3 studies of ART initiation in treatment-naive patients in which serial whole-body dual-energy X-ray absorptiometry scans were performed. They used linear regression to evaluate effects of baseline CD4(+) and 16-week CD4(+) change (both absolute and relative) on

96-week total BMD change from baseline. They performed multivariable linear regression to assess associations between baseline variables of age, sex, race/ethnicity, body mass index (BMI), hepatitis C status, parent study, human immunodeficiency virus type 1 (HIV-1) RNA level, and assignment to a protease inhibitor (PI)- or tenofovir-containing regimen on 96-week total BMD change. The included 796 subjects had mean 96-week total BMD loss of 2.0%. In multivariable analysis, baseline CD4(+) cell count was significantly associated with 96-week BMD loss; individuals with baseline CD4(+) <50 cells/μL lost significantly more BMD compared to those with CD4(+) ≥500 cells/μL. A greater relative, but not absolute, 16-week increase in CD4(+) count was significantly associated with greater declines in BMD, but not after controlling for baseline CD4(+) count. In multivariable analysis, older age, female sex, lower BMI, higher HIV-1 RNA levels, and PI and tenofovir assignment were also associated with greater BMD decline. Low pretreatment CD4(+) count, but not greater CD4(+) count increase, is a strong and independent risk factor for bone loss after ART initiation. ART initiation at higher CD4(+) counts may reduce the burden of osteoporosis and fragility fractures.

Substance Use Disorders: Psychoneuroimmunological Mechanisms and New Targets For Therapy. Loftis JM, Huckans M. Pharmacol Ther 2013; 139(2): 289-300.
An estimated 76.4 million people worldwide meet criteria for alcohol use disorders, and 15.3 million meet criteria for drug use disorders. Given the high rates of addiction and the associated health, economic, and social costs, it is essential to develop a thorough understanding of the impact of substance abuse on mental and physical health outcomes and to identify new treatment approaches for substance use disorders (SUDs). Psychoneuroimmunology is a rapidly expanding, multidisciplinary area of research that may be of particular importance to addiction medicine, as its focus is on the dynamic and complex interactions among behavioral factors, the central nervous system, and the endocrine and immune systems (Ader, 2001). This review, therefore, focuses on: 1) the psychoneuroimmunologic effects of SUDs by substance type and use pattern, and 2) the current and future treatment strategies, including barriers that can impede successful recovery outcomes. Evidence-based psychosocial and pharmacotherapeutic treatments are reviewed. Psychological factors and central nervous system correlates that impact treatment adherence and response are discussed. Several novel therapeutic approaches that are currently under investigation are introduced; translational data from animal and human studies is presented, highlighting immunotherapy as a promising new direction for addiction medicine.

HIV-1 Infection Of Hematopoietic Progenitor Cells In Vivo In Humanized Mice. Nixon CC, Vatakis DN, Reichelderfer SN, Dixit D, Kim SG, Uittenbogaart CH, Zack JA. Blood 2013; 122(13): 2195-2204.
HIV infection has been associated with defective hematopoiesis since the earliest days of the HIV/AIDS epidemic. Generation of all hematopoietic lineages suffers in the face of infection. The mechanisms by which HIV impairs normal blood cell development remain unclear, and direct infection of intermediate hematopoietic progenitors has not been established as a source of HIV-associated hematopoietic pathology. Here, the authors demonstrate infection of multiple subsets of highly purified intermediate hematopoietic progenitors by wild-type HIV both in vitro and in vivo. Although direct infection is clearly cytotoxic, the authors find that some infected progenitors can survive and harbor proviral DNA. They report intermediate hematopoietic progenitors to be a novel target of infection and their permissivity to infection increases with development. Further, the nonobese diabetic severe combined immunodeficiency common γ chain knockout-bone marrow-liver-thymus humanized mouse provides a unique model for studying the impact of HIV infection on bone marrow-based human hematopoiesis.

Ion Selectivity and Gating Mechanisms Of FNT Channels. Waight AB, Czyzewski BK, Wang DN. Curr Opin Struct Biol 2013; 23(4): 499-506.
The phospholipid bilayer has evolved to be a protective and selective barrier by which the cell maintains high concentrations of life sustaining organic and inorganic material. As gatekeepers responsible for an immense amount of bidirectional chemical traffic between the cytoplasm and extracellular milieu, ion channels have been studied in detail since their postulated existence nearly three-quarters of a century ago. Over the past fifteen years, we have begun to understand how selective permeability can be achieved for both cationic and anionic ions. Our mechanistic knowledge has expanded recently with studies of a large family of anion channels, the Formate Nitrite Transport (FNT) family. This family has proven amenable to structural studies at a resolution high enough to reveal intimate details of ion selectivity and gating. With five representative members having yielded a total of 15 crystal structures, this family represents one of the richest sources of structural information for anion channels.

Rats Classified As Low Or High Cocaine Locomotor Responders: A Unique Model Involving Striatal Dopamine Transporters That Predicts Cocaine Addiction-Like Behaviors. Yamamoto DJ, Nelson AM, Mandt BH, Larson GA, Rorabaugh JM, Ng CMC, Barcomb KM, Richards TL, Allen RM, Zahniser NR. Neurosci Biobehav Rev 2013; 37(8): 1738-1753.
Individual differences are a hallmark of drug addiction. Here, the authors describe a rat model based on differential initial responsiveness to low dose cocaine. Despite similar brain cocaine levels, individual outbred Sprague-Dawley rats exhibit markedly different magnitudes of acute cocaine-induced locomotor activity and, thereby, can be classified as low or high cocaine responders (LCRs or HCRs). LCRs and HCRs differ in drug-induced, but not novelty-associated, hyperactivity. LCRs have higher basal numbers of striatal dopamine transporters (DATs) than HCRs and exhibit marginal cocaine inhibition of in vivo DAT activity and cocaine-induced increases in extracellular DA. Importantly, lower initial cocaine response predicts greater locomotor sensitization, conditioned place preference and greater motivation to self-administer cocaine following low dose acquisition. Further, outbred Long-Evans rats classified as LCRs, versus HCRs, are more sensitive to cocaine's discriminative stimulus effects. Overall, results to date with the LCR/HCR model underscore the contribution of striatal DATs to individual differences in initial cocaine responsiveness and the value of assessing the influence of initial drug response on subsequent expression of addiction-like behaviors.

Dynamics Of DNA Methylation In Recent Human and Great Ape Evolution. Hernando-Herraez I, Prado-Martinez J, Garg P, Fernandez-Callejo M, Heyn H, Hvilsom C, Navarro A, Esteller M, Sharp AJ, Marques-Bonet T. PLoS Genet 2013; 9(9): e1003763.
DNA methylation is an epigenetic modification involved in regulatory processes such as cell differentiation during development, X-chromosome inactivation, genomic imprinting and susceptibility to complex disease. However, the dynamics of DNA methylation changes between humans and their closest relatives are still poorly understood. The authors performed a comparative analysis of CpG methylation patterns between 9 humans and 23 primate samples including all species of great apes (chimpanzee, bonobo, gorilla and orangutan) using Illumina Methylation450 bead arrays. This analysis identified ~800 genes with significantly altered methylation patterns among the great apes, including ~170 genes with a methylation pattern unique to human. Some of these are known to be involved in developmental and neurological features, suggesting that epigenetic changes have been frequent during recent human and primate evolution. The authors identified a significant positive relationship between the rate of coding variation and alterations of methylation at the promoter level, indicative of co-occurrence between evolution of protein

sequence and gene regulation. In contrast, and supporting the idea that many phenotypic differences between humans and great apes are not due to amino acid differences, this analysis also identified 184 genes that are perfectly conserved at protein level between human and chimpanzee, yet show significant epigenetic differences between these two species. The authors conclude that epigenetic alterations are an important force during primate evolution and have been under-explored in evolutionary comparative genomics.

Widespread Dysregulation Of Peptide Hormone Release In Mice Lacking Adaptor Protein AP-3. Sirkis DW, Edwards RH, Asensio CS. PLoS Genet 2013; 9(9): e1003812.
The regulated secretion of peptide hormones, neural peptides and many growth factors depends on their sorting into large dense core vesicles (LDCVs) capable of regulated exocytosis. LDCVs form at the trans-Golgi network, but the mechanisms that sort proteins to this regulated secretory pathway and the cytosolic machinery that produces LDCVs remain poorly understood. Recently, the authors used an RNAi screen to identify a role for heterotetrameric adaptor protein AP-3 in regulated secretion and in particular, LDCV formation. Indeed, mocha mice lacking AP-3 have a severe neurological and behavioral phenotype, but this has been attributed to a role for AP-3 in the endolysosomal rather than biosynthetic pathway. The authors therefore used mocha mice to determine whether loss of AP-3 also dysregulates peptide release in vivo. They find that adrenal chromaffin cells from mocha animals show increased constitutive exocytosis of both soluble cargo and LDCV membrane proteins, reducing the response to stimulation. They also observe increased basal release of both insulin and glucagon from pancreatic islet cells of mocha mice, suggesting a global disturbance in the release of peptide hormones. AP-3 exists as both ubiquitous and neuronal isoforms, but the analysis of mice lacking each of these isoforms individually and together shows that loss of both is required to reproduce the effect of the mocha mutation on the regulated pathway. In addition, the authors show that loss of the related adaptor protein AP-1 has a similar effect on regulated secretion but exacerbates the effect of AP-3 RNAi, suggesting distinct roles for the two adaptors in the regulated secretory pathway.

B-Arrestin Protects Neurons By Mediating Endogenous Opioid Arrest Of Inflammatory Microglia. Feng X, Wu CY, Burton FH, Loh HH, Wei LN. Cell Death Differ 2013.
Microglial activation worsens neuronal loss and contributes to progressive neurological diseases like Parkinson's disease (PD). This inflammatory progression is countered by dynorphin (Dyn), the endogenous ligand of the kappa-opioid receptor (KOR). The authors show that microglial β-arrestin mediates the ability of Dyn/KOR to limit endotoxin-elicited production of pro-inflammatory effectors and cytokines, subsequently protecting neurons from inflammation-induced neurotoxicity. Agonist-activated KOR enhances the interaction of β-arrestin2 with transforming growth factor-beta-activated kinase 1 (TAK1)-binding protein 1 (TAB1), disrupting TAK1-TAB1 mediated pro-inflammatory gene expression. The authors reveal a new physiological role for β-arrestin in neuroprotection via receptor internalization-triggered blockade of signal effectors of microglial inflammatory neurotoxicity. This result offers novel drug targets in the convergent KOR/β-arrestin2 and inflammatory pathways for treating microglial inflammatory neuropathologies like PD.

Prenatal Cocaine Exposure and Gray Matter Volume In Adolescent Boys and Girls: Relationship To Substance Use Initiation. Rando K, Chaplin TM, Potenza MN, Mayes L, Sinha R. Biol Psychiatry 2013; 74(7): 482-489.
Studies of prenatal cocaine exposure have primarily examined childhood populations. Studying adolescents is especially important because adolescence is a time of changing motivations and initiation of substance use. Using magnetic resonance imaging and whole-brain voxel-based

morphometry, the authors assessed gray matter volume (GMV) differences in 42 prenatally cocaine exposed (PCE) and 21 noncocaine-exposed (NCE) adolescents, aged 14 to 17 years. Associations between GMV differences in significant clusters and the probability of substance use initiation were examined. PCE relative to NCE adolescents demonstrated three clusters of lower GMV involving a limbic and paralimbic ($p < .001$, family-wise error [FWE] corrected), superior frontal gyrus ($p = .001$, FWE corrected), and precuneus ($p = .019$, FWE corrected) cluster. GMVs in the superior frontal and precuneus clusters were associated with initiation of substance use. Each 1-mL decrease in GMV increased the probability of initiating substance use by 69.6% ($p = .01$) in the superior frontal cluster and 83.6% ($p = .02$) in the precuneus cluster. The authors conclude that PCE is associated with structural differences in cortical and limbic regions. Lower GMVs in frontal cortical and posterior regions are associated with substance use initiation and may represent biological risk markers for substance use.

Kappa Opioid Receptor-Mediated Dysregulation Of Gamma-Aminobutyric Acidergic Transmission In The Central Amygdala In Cocaine Addiction. Kallupi M, Wee S, Edwards S, Whitfield Jr TW, Oleata CS, Luu G, Schmeichel BE, Koob GF, Roberto M. Biol Psychiatry 2013; 74(7): 520-528.

Studies have demonstrated an enhanced dynorphin/kappa-opioid receptor (KOR) system following repeated cocaine exposure, but few reports have focused on neuroadaptations within the central amygdala (CeA). The authors identified KOR-related physiological changes in the CeA following escalation of cocaine self-administration in rats. They used in vitro slice electrophysiological (intracellular and whole-cell recordings) methods to assess whether differential cocaine access in either 1-hour (short access [ShA]) or 6-hour (long access [LgA]) sessions induced plasticity at CeA gamma-aminobutyric acid (GABA)ergic synapses or altered the sensitivity of these synapses to KOR agonism (U50488) or antagonism (norbinaltorphimine [norBNI]). They then determined the functional effects of CeA KOR blockade in cocaine-related behaviors. Baseline evoked GABAergic transmission was enhanced in the CeA from ShA and LgA rats compared with cocaine-naïve rats. Acute cocaine (1 μmol/L) application significantly decreased GABA release in all groups (naïve, ShA, and LgA rats). Application of U50488 (1 μmol/L) significantly decreased GABAergic transmission in the CeA from naïve rats but increased it in LgA rats. Conversely, norBNI (200 nmol/L) significantly increased GABAergic transmission in the CeA from naïve rats but decreased it in LgA rats. Norbinaltorphimine did not alter the acute cocaine-induced inhibition of GABAergic responses. Finally, CeA microinfusion of norBNI blocked cocaine-induced locomotor sensitization and attenuated the heightened anxiety-like behavior observed during withdrawal from chronic cocaine exposure in the defensive burying paradigm. Together these data demonstrate that CeA dynorphin/KOR systems are dysregulated following excessive cocaine exposure and suggest KOR antagonism as a viable therapeutic strategy for cocaine addiction.

Methamphetamine-Associated Memory Is Regulated by a Writer and an Eraser of Permissive Histone Methylation. Aguilar-Valles A, Vaissiere T, Griggs EM, Mikaelsson MA, Takacs IF, Young EJ, Rumbaugh G, Miller CA. Biol Psychiatry 2013.

Memories associated with drugs of abuse, such as methamphetamine (METH), increase relapse vulnerability to substance use disorder by triggering craving. The nucleus accumbens (NAc) is essential to these drug-associated memories, but underlying mechanisms are poorly understood. Posttranslational chromatin modifications, such as histone methylation, modulate gene transcription; thus, the authors investigated the role of the associated epigenetic modifiers in METH-associated memory. Conditioned place preference was used to assess the epigenetic landscape in the NAc supporting METH-associated memory ($n = 79$). The impact of histone

methylation (H3K4me2/3) on the formation and expression of METH-associated memory was determined by focal, intra-NAc knockdown (KD) of a writer, the methyltransferase mixed-lineage leukemia 1 (Mll1) (n = 26), and an eraser, the histone lysine (K)-specific demethylase 5C (Kdm5c) (n = 38), of H3K4me2/3. A survey of chromatin modifications in the NAc of animals forming a METH-associated memory revealed the global induction of several modifications associated with active transcription. This correlated with a pattern of gene activation, as revealed by microarray analysis, including upregulation of oxytocin receptor (Oxtr) and FBJ osteosarcoma oncogene (Fos), the promoters of which also had increased H3K4me3. KD of Mll1 reduced H3K4me3, Fos and Oxtr levels and disrupted METH-associated memory. KD of Kdm5c resulted in hypermethylation of H3K4 and prevented the expression of METH-associated memory. The development and expression of METH-associated memory are supported by regulation of H3K4me2/3 levels by MLL1 and KDM5C, respectively, in the NAc. These data indicate that permissive histone methylation, and the associated epigenetic writers and erasers, represent potential targets for the treatment of substance abuse relapse, a psychiatric condition perpetuated by unwanted associative memories.

Selective, Retrieval-Independent Disruption of Methamphetamine-Associated Memory by Actin Depolymerization. Young EJ, Aceti M, Griggs EM, Fuchs RA, Zigmond Z, Rumbaugh G, Miller CA. Biol Psychiatry 2013.

Memories associated with drugs of abuse, such as methamphetamine (METH), increase relapse vulnerability to substance use disorder. There is a growing consensus that memory is supported by structural and functional plasticity driven by F-actin polymerization in postsynaptic dendritic spines at excitatory synapses. However, the mechanisms responsible for the long-term maintenance of memories, after consolidation has occurred, are largely unknown. Conditioned place preference (n = 112) and context-induced reinstatement of self-administration (n = 19) were used to assess the role of F-actin polymerization and myosin II, a molecular motor that drives memory-promoting dendritic spine actin polymerization, in the maintenance of METH-associated memories and related structural plasticity. Memories formed through association with METH but not associations with foot shock or food reward were disrupted by a highly-specific actin cycling inhibitor when infused into the amygdala during the postconsolidation maintenance phase. This selective effect of depolymerization on METH-associated memory was immediate, persistent, and did not depend upon retrieval or strength of the association. Inhibition of non-muscle myosin II also resulted in a disruption of METH-associated memory. Thus, drug-associated memories seem to be actively maintained by a unique form of cycling F-actin driven by myosin II. This finding provides a potential therapeutic approach for the selective treatment of unwanted memories associated with psychiatric disorders that is both selective and does not rely on retrieval of the memory. The results further suggest that memory maintenance depends upon the preservation of polymerized actin.

Genome-Wide Association Study Identifies New Susceptibility Loci For Posttraumatic Stress Disorder. Xie P, Kranzler HR, Yang C, Zhao H, Farrer LA, Gelernter J. Biol Psychiatry 2013; 74(9): 656-663.

Genetic factors influence the risk for posttraumatic stress disorder (PTSD), a potentially chronic and disabling psychiatric disorder that can arise after exposure to trauma. Candidate gene association studies have identified few genetic variants that contribute to PTSD risk. The authors conducted genome-wide association analyses in 1578 European Americans (EAs), including 300 PTSD cases, and 2766 African Americans, including 444 PTSD cases, to find novel common risk alleles for PTSD. They used the Illumina Omni1-Quad microarray, which yielded approximately 870,000 single nucleotide polymorphisms (SNPs) suitable for analysis. In EAs, the authors observed that one

SNP on chromosome 7p12, rs406001, exceeded genome-wide significance (p = 3.97 × 10(-8)). A SNP that maps to the first intron of the Tolloid-Like 1 gene (TLL1) showed the second strongest evidence of association, although no SNPs at this locus reached genome-wide significance. The authors then tested six SNPs in an independent sample of nearly 2000 EAs and successfully replicated the association findings for two SNPs in the first intron of TLL1, rs6812849 and rs7691872, with p values of 6.3 × 10(-6) and 2.3 × 10(-4), respectively. In the combined sample, rs6812849 had a p value of 3.1×10(-9). No significant signals were observed in the African American part of the sample. Genome-wide association study analyses restricted to trauma-exposed individuals yielded very similar results. This study identified TLL1 as a new susceptibility gene for PTSD.

Genome-Wide Association Study of Opioid Dependence: Multiple Associations Mapped to Calcium and Potassium Pathways. Gelernter J, Kranzler HR, Sherva R, Koesterer R, Almasy L, Zhao H, Farrer LA. Biol Psychiatry 2013.

The authors report a genome-wide association study (GWAS) of two populations, African-American and European-American (AA, EA) for opioid dependence (OD) in three sets of subjects, to identify pathways, genes, and alleles important in OD risk. The design employed three phases (on the basis of separate sample collections). Phase 1 included the authors' discovery GWAS dataset consisting of 5697 subjects (58% AA) diagnosed with opioid and/or other substance dependence and control subjects. Subjects were genotyped with the Illumina OmniQuad microarray, yielding 890,000 single nucleotide polymorphisms (SNPs) suitable for analysis. Additional genotypes were imputed with the 1000 Genomes reference panel. Top-ranked findings were further evaluated in Phase 2 by incorporating information from the publicly available Study of Addiction: Genetics and Environment dataset, with GWAS data from 4063 subjects (32% AA). In Phase 3, the most significant SNPs from Phase 2 were genotyped in 2549 independent subjects (32% AA). Analyses were performed with case-control and ordinal trait designs. Most significant results emerged from the AA subgroup. Genome-wide-significant associations ($p < 5.0 \times 10^{-8}$) were observed with SNPs from multiple loci-KCNG2*rs62103177 was most significant after combining results from datasets in every phase of the study. The most compelling results were obtained with genes involved in potassium signaling pathways (e.g., KCNC1 and KCNG2). Pathway analysis also implicated genes involved in calcium signaling and long-term potentiation. This is the first study to identify risk variants for OD with GWAS. These results strongly implicate risk pathways and provide insights into novel therapeutic and prevention strategies and might biologically bridge OD and other non-substance dependence psychiatric traits where similar pathways have been implicated.

ELK1 Transcription Factor Linked To Dysregulated Striatal Mu Opioid Receptor Signaling Network and OPRM1 Polymorphism In Human Heroin Abusers. Sillivan SE, Whittard JD, Jacobs MM, Ren Y, Mazloom AR, Caputi FF, Horvath M, Keller E, Ma'ayan A, Pan YX, Chiang LW, Hurd YL. Biol Psychiatry 2013; 74(7): 511-519.

Abuse of heroin and prescription opiate medications has grown to disturbing levels. Opioids mediate their effects through mu opioid receptors (MOR), but minimal information exists regarding MOR-related striatal signaling relevant to the human condition. The striatum is a structure central to reward and habitual behavior and neurobiological changes in this region are thought to underlie the pathophysiology of addiction disorders. The authors examined molecular mechanisms related to MOR in postmortem human brain striatal specimens from a homogenous European Caucasian population of heroin abusers and control subjects and in an animal model of heroin self-administration. Expression of ets-like kinase 1 (ELK1) was examined in relation to polymorphism of the MOR gene OPRM1 and drug history. A characteristic feature of heroin abusers was

decreased expression of MOR and extracellular regulated kinase signaling networks, concomitant with dysregulation of the downstream transcription factor ELK1. Striatal ELK1 in heroin abusers associated with the polymorphism rs2075572 in OPRM1 in a genotype dose-dependent manner and correlated with documented history of heroin use, an effect reproduced in an animal model that emphasizes a direct relationship between repeated heroin exposure and ELK1 dysregulation. A central role of ELK1 was evidenced by an unbiased whole transcriptome microarray that revealed ~20% of downregulated genes in human heroin abusers are ELK1 targets. Using chromatin immune precipitation, the authors confirmed decreased ELK1 promoter occupancy of the target gene Use1. ELK1 is a potential key transcriptional regulatory factor in striatal disturbances associated with heroin abuse and relevant to genetic mutation of OPRM1.

How Might Circadian Rhythms Control Mood? Let Me Count The Ways... McClung CA. Biol Psychiatry 2013; 74(4): 242-249.
Mood disorders are serious diseases that affect a large portion of the population. There have been many hypotheses put forth over the years to explain the development of major depression, bipolar disorder, and other mood disorders. These hypotheses include disruptions in monoamine transmission, hypothalamus-pituitary-adrenal axis function, immune function, neurogenesis, mitochondrial dysfunction, and neuropeptide signaling (to name a few). Nearly all people suffering from mood disorders have significant disruptions in circadian rhythms and the sleep/wake cycle. In fact, altered sleep patterns are one of the major diagnostic criteria for these disorders. Moreover, environmental disruptions to circadian rhythms, including shift work, travel across time zones, and irregular social schedules, tend to precipitate or exacerbate mood-related episodes. Recent studies have found that molecular clocks are found throughout the brain and body where they participate in the regulation of most physiological processes, including those thought to be involved in mood regulation. This review will summarize recent data that implicate the circadian system as a vital regulator of a variety of systems that are thought to play a role in the development of mood disorders.

5-Lipoxygenase Activating Protein Reduction Ameliorates Cognitive Deficit, Synaptic Dysfunction, and Neuropathology In A Mouse Model Of Alzheimer's Disease. Giannopoulos PF, Chu J, Joshi YB, Sperow M, Li JG, Kirby LG, Pratico D. Biol Psychiatry 2013; 74(5): 348-356.
5-lipoxygenase activating protein (FLAP) is abundantly present in the central nervous system. Although its function has been extensively interrogated in the context of peripheral inflammation, novel roles for this protein are emerging in the central nervous system. The objective of this study was to investigate the functional role that FLAP plays in a mouse model of Alzheimer's disease (AD) with plaques and tangles (i.e., 3xTg mice). By implementing a genetic knockout of FLAP and pharmacologic inhibition with a FLAP inhibitor (MK-591), the authors evaluated the effect on the AD-like neuropathology, cognition, and synaptic plasticity in the 3xTg mice. They show that reduction of FLAP leads to amelioration of cognition and memory along with the rescuing of synaptic dysfunction at an early age before the development of overt neuropathology. Genetic knockout and pharmacologic inhibition of FLAP also yielded an improvement in AD pathology through a reduction in Aβ via the γ-secretase pathway and a decrease in tau phosphorylation through the cdk5 pathway. These studies identify a novel functional role for FLAP in regulating memory and synaptic plasticity. They establish this protein at the crossroad of multiple pathways that ultimately contribute to the development of the entire AD-like phenotype, making it a viable therapeutic target with disease-modifying capacity for the treatment of this disease.

Endocannabinoids Promote Cocaine-Induced Impulsivity and Its Rapid Dopaminergic Correlates. Hernandez G, Oleson EB, Gentry RN, Abbas Z, Bernstein DL, Arvanitogiannis A, Cheer JF. Biol Psychiatry 2013.

Impaired decision making, a hallmark of addiction, is hypothesized to arise from maladaptive plasticity in the mesolimbic dopamine pathway. The endocannabinoid system modulates dopamine activity through activation of cannabinoid type 1 receptors (CB1Rs). Here, the authors investigated whether impulsive behavior observed following cocaine exposure requires CB1R activation. They trained rats in a delay-discounting task. Following acquisition of stable performance, rats were exposed to cocaine (10 mg/kg, intraperitoneal) every other day for 14 days and locomotor activity was measured. Two days later, delay-discounting performance was re-evaluated. To assess reversal of impulsivity, injections of a CB1R antagonist (1.5 mg/kg, intraperitoneal) or vehicle were given 30 minutes before the task. During the second experiment, aimed at preventing impulsivity rather than reversing it, CB1Rs were antagonized before each cocaine injection. In this experiment, subsecond dopamine release was measured in the nucleus accumbens during delay-discounting sessions before and after cocaine treatment. Blockade of CB1Rs reversed and prevented cocaine-induced impulsivity. Electrochemical results showed that during baseline and following disruption of endocannabinoid signaling, there was a robust increase in dopamine for immediate large rewards compared with immediate small rewards, but this effect reversed when the delay for the large reward was 10 seconds. In contrast, dopamine release always increased for one-pellet options at minimal or moderate delays in vehicle-treated rats. The authors conclude that endocannabinoids play a critical role in changes associated with cocaine exposure. Cannabinoid type 1 receptor blockade may thus counteract maladaptive alterations in afferents to dopamine neurons, thereby preventing changes in dopaminergic activity underlying a loss of self-control.

Striatal-Enriched Protein Tyrosine Phosphatase-STEPs Toward Understanding Chronic Stress-Induced Activation of Corticotrophin Releasing Factor Neurons in the Rat Bed Nucleus of the Stria Terminalis. Dabrowska J, Hazra R, Guo JD, Li C, Dewitt S, Xu J, Lombroso PJ, Rainnie DG. Biol Psychiatry 2013; 74(11): 817-826.

Striatal-enriched protein tyrosine phosphatase (STEP) is a brain-specific protein tyrosine phosphatase that opposes the development of synaptic strengthening and the consolidation of fear memories. In contrast, stress facilitates fear memory formation, potentially by activating corticotrophin releasing factor (CRF) neurons in the anterolateral cell group of the bed nucleus of the stria terminalis (BNSTALG). Here, using dual-immunofluorescence, single-cell reverse transcriptase polymerase chain reaction, quantitative reverse transcriptase polymerase chain reaction, Western blot, and whole-cell patch-clamp electrophysiology, the authors examined the expression and role of STEP in regulating synaptic plasticity in rat BNSTALG neurons and its modulation by stress. Striatal-enriched protein tyrosine phosphatase was selectively expressed in CRF neurons in the oval nucleus of the BNSTALG. Following repeated restraint stress (RRS), animals displayed a significant increase in anxiety-like behavior, which was associated with a downregulation of STEP messenger RNA and protein expression in the BNSTALG, as well as selectively enhancing the magnitude of long-term potentiation (LTP) induced in Type III, putative CRF neurons. To determine if the changes in STEP expression following RRS were mechanistically related to LTP facilitation, the authors examined the effects of intracellular application of STEP on the induction of LTP. STEP completely blocked the RRS-induced facilitation of LTP in BNSTALG neurons. Hence, STEP acts to buffer CRF neurons against excessive activation, while downregulation of STEP after chronic stress may result in pathologic activation of CRF neurons in the BNSTALG and contribute to prolonged states of anxiety. Thus, targeted manipulations of STEP activity might represent a novel treatment strategy for stress-induced anxiety disorders.

Sex Differences in Sensitivity to the Depressive-like Effects of the Kappa Opioid Receptor Agonist U-50488 in Rats. Russell SE, Rachlin AB, Smith KL, Muschamp J, Berry L, Zhao Z, Chartoff EH. Biol Psychiatry 2013.
Dynorphin, an endogenous ligand at kappa opioid receptors (KORs), produces depressive-like effects and contributes to addictive behavior in male nonhuman primates and rodents. Although comorbidity of depression and addiction is greater in women than men, the role of KORs in female motivated behavior is unknown. In adult Sprague-Dawley rats, the authors used intracranial self-stimulation to measure effects of the KOR agonist (±)-trans-U-50488 methanesulfonate salt (U-50488) (.0-10.0 mg/kg) on brain stimulation reward in gonadally intact and castrated males and in females at estrous cycle stages associated with low and high estrogen levels. Pharmacokinetic studies of U-50488 in plasma and brain were conducted. Immunohistochemistry was used to identify sex-dependent expression of U-50488-induced c-Fos in brain. U-50488 dose-dependently increased the frequency of stimulation (threshold) required to maintain intracranial self-stimulation responding in male and female rats, a depressive-like effect. However, females were significantly less sensitive than males to the threshold-increasing effects of U-50488, independent of estrous cycle stage in females or gonadectomy in males. Although initial plasma concentrations of U-50488 were higher in females, there were no sex differences in brain concentrations. Sex differences in U-50488-induced c-Fos activation were observed in corticotropin releasing factor-containing neurons of the paraventricular nucleus of the hypothalamus and primarily in non-corticotropin releasing factor-containing neurons of the bed nucleus of the stria terminalis. These data suggest that the role of KORs in motivated behavior of rats is sex-dependent, which has important ramifications for the study and treatment of mood-related disorders, including depression and drug addiction in people.

Density-Dependent Cooperative Non-Specific Binding In Solid-Phase SELEX Affinity Selection. Ozer A, White BS, Lis JT, Shalloway D. Nucleic Acids Res 2013; 41(14): 7167-7175.
The non-specific binding of undesired ligands to a target is the primary factor limiting the enrichment of tight-binding ligands in affinity selection. Solution-phase non-specific affinity is determined by the free-energy of ligand binding to a single target. However, the solid-phase affinity might be higher if a ligand bound concurrently to multiple adjacent immobilized targets in a cooperative manner. Cooperativity could emerge in this case as a simple consequence of the relationship between the free energy of binding, localization entropy and the spatial distribution of the immobilized targets. The authors tested this hypothesis using a SELEX experimental design and found that non-specific RNA aptamer ligands can concurrently bind up to four bead-immobilized peptide targets, and that this can increase their effective binding affinity by two orders-of-magnitude. Binding curves were quantitatively explained by a new statistical mechanical model of density-dependent cooperative binding, which relates cooperative binding to both the target concentration and the target surface density on the immobilizing substrate. Target immobilization plays a key role in SELEX and other ligand enrichment methods, particularly in new multiplexed microfluidic purification devices, and these results have strong implications for optimizing their performance.

Identifying the Targets Of Aminoacyl-Trna Synthetase Inhibitors By Primer Extension Inhibition. Orelle C, Szal T, Klepacki D, Shaw KJ, Vazquez-Laslop N, Mankin AS. Nucleic Acids Res 2013; 41(14): e144.
Aminoacyl-transfer RNA (tRNA) synthetases (RS) are essential components of the cellular translation machinery and can be exploited for antibiotic discovery. Because cells have many different RS, usually one for each amino acid, identification of the specific enzyme targeted by a new natural or synthetic inhibitor can be cumbersome. The authors describe the use of the primer

extension technique in conjunction with specifically designed synthetic genes to identify the RS targeted by an inhibitor. Suppression of a synthetase activity reduces the amount of the cognate aminoacyl-tRNA in a cell-free translation system resulting in arrest of translation when the corresponding codon enters the decoding center of the ribosome. The utility of the technique is demonstrated by identifying a switch in target specificity of some synthetic inhibitors of threonyl-tRNA synthetase.

Amylin Receptor Signaling In the Ventral Tegmental Area Is Physiologically Relevant For the Control Of Food Intake. Mietlicki-Baase EG, Rupprecht LE, Olivos DR, Zimmer DJ, Alter MD, Pierce RC, Schmidt HD, Hayes MR. Neuropsychopharmacology 2013; 38(9): 1685-1697.
The ability of amylin, a pancreatic β-cell-derived neuropeptide, to promote negative energy balance has been ascribed to neural activation at the area postrema. However, despite amylin binding throughout the brain, the possible role of amylin signaling at other nuclei in the control of food intake has been largely neglected. The authors show that mRNA for all components of the amylin receptor complex is expressed in the ventral tegmental area (VTA), a mesolimbic structure mediating food intake and reward. Direct activation of VTA amylin receptors reduces the intake of chow and palatable sucrose solution in rats. This effect is mediated by reductions in meal size and is not due to nausea/malaise or prolonged suppression of locomotor activity. VTA amylin receptor activation also reduces sucrose self-administration on a progressive ratio schedule. Finally, antagonist studies provide novel evidence that VTA amylin receptor blockade increases food intake and attenuates the intake-suppressive effects of a peripherally administered amylin analog, suggesting that amylin receptor signaling in the VTA is physiologically relevant for food intake control and potentially clinically relevant for the treatment of obesity.

Disruption of Glutamate Receptor-Interacting Protein in Nucleus Accumbens Enhances Vulnerability to Cocaine Relapse. Briand LA, Kimmey BA, Ortinski PI, Huganir RL, Pierce RC. Neuropsychopharmacology 2013.
Trafficking and stabilization of AMPA receptors at synapses in response to cocaine exposure is thought to be critical for expression of cocaine addiction and relapse. Glutamate receptor-interacting protein (GRIP) is a neuronal scaffolding protein that stabilizes GluA2 AMPARs at synapses but its role in cocaine addiction has not been examined. The current study demonstrates that conditional deletion of GRIP within the nucleus accumbens potentiates cue-induced reinstatement of cocaine seeking without affecting operant learning, locomotor activity, or reinstatement of natural reward seeking. This is the first study to demonstrate a role for accumbal GRIP in behavior. Electrophysiological recordings revealed increased rectification of AMPAR-mediated currents in the nucleus accumbens and increased AMPAR sensitivity to the GluA2-lacking AMPAR antagonist, 1-naphthylacetyl spermine, indicative of an increased contribution of GluA2-lacking calcium-permeable AMPARs. In addition, accumbal GRIP deletion was associated with blunted long-term depression, similar to what is seen following cocaine self-administration. Taken together, these results indicate that GRIP may modulate addictive phenotypes through its regulation of synaptic AMPARs by controlling their subunit composition and susceptibility to LTD. These effects are associated with changes in vulnerability to cocaine relapse and highlight GRIP as a novel target for the development of cocaine addiction therapeutics.

Neural Correlates Of Impulsivity In Healthy Males and Females With Family Histories Of Alcoholism. Devito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH, Pearlson GD. Neuropsychopharmacology 2013; 38(10): 1854-1863.

Individuals family-history positive (FHP) for alcoholism have increased risk for the disorder, which may be mediated by intermediate behavioral traits such as impulsivity. Given the sex differences in the risk for and clinical presentation of addictive disorders, risk for addiction may be differentially mediated by impulsivity within FHP males and females. FHP (N=28) and family-history negative (FHN, N=31) healthy, non-substance-abusing adults completed an fMRI Go/No-Go task and were assessed on impulsivity and alcohol use. Effects of family history and sex were investigated as were associations between neural correlates of impulse control and out-of-scanner measures of impulsivity and alcohol use. FHP individuals showed greater activation in the left anterior insula and inferior frontal gyrus during successful inhibitions, an effect that was driven primarily by FHP males. Higher self-reported impulsivity and behavioral discounting impulsivity, but not alcohol use measures, were associated with greater BOLD signal in the region that differentiated the FHP and FHN groups. Impulsivity factors were associated with alcohol use measures across the FHP and FHN groups. These findings are consistent with increased risk for addiction among FHP individuals being conferred through disrupted function within neural systems important for impulse control.

NEW RESOURCES, REAGENTS, AND DATABASES

Characterization Of An Agonist Probe For Opioid Receptor Mu 1 (OPRM1)-Opioid Receptor Delta 1 (OPRD1) Heterodimerization. Pinello C, Guerrero M, Eberhart C, Volmar CH, Saldanha SA, Cayanan C, Urbano M, Brown SJ, Ferguson J, Gomes I, Devi LA, Roberts E, Hodder P, Rosen H. Probe Reports from the NIH Molecular Libraries Program [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2010-2012 Dec 17 [updated 2013 Apr 5].

Opiates such as morphine are the choice analgesic in the treatment of chronic pain due to their potent and rapid action. Opioid receptors belong to the family of G protein-coupled receptors (GPCRs), one of the largest gene families in the mammalian genome. The OPRM1 gene encodes the mu opioid receptor, which is the primary site of action for morphine and other commonly used opioids such as heroin, fentanyl, and methadone. The long-term use of opiates is limited because of the development of tolerance and dependence, as well as respiratory suppression and constipation. Due to their clinical importance, various strategies have been considered for making opiates more effective while curbing liabilities such as addiction. One such strategy has been to use a combination of drugs to improve the effectiveness of morphine. In particular, delta opioid receptor (OPRD1) ligands have been useful in enhancing morphine's potency, but the underlying molecular basis is not understood. It has been shown that modulation of receptor function by physical association between OPRM1 and OPRD1 is a potential mechanism; heteromerization of OPRM1 with OPRD1 leads to the modulation of receptor binding and signaling properties. It has further been shown that the selective activation of the OPRM1-OPRD1 heteromer by a combination of OPRM1 agonist with OPRD1 antagonist can be blocked by antibodies that selectively recognize the heteromer. Therefore, the identification of compounds that selectively activate OPRM1-OPRD1 heterodimerization may have potential in the treatment of pain and alleviate unwanted effects associated with opiate use. The Scripps Research Institute Molecular Screening Center (SRIMSC), part of the Molecular Libraries Probe Production Centers Network (MLPCN), reports here an agonist for OPRM1-OPRD1 heterdimerization, ML335, with an EC50 of 403 nM, and selectivities vs. OPRM1, OPRD1, and HTR5A of 37, 2.7, and >99, respectively.

The Crapome: A Contaminant Repository For Affinity Purification-Mass Spectrometry Data. Mellacheruvu D, Wright Z, Couzens AL, Lambert JP, St-Denis NA, Li T, Miteva YV, Hauri S, Sardiu ME, Low TY, Halim VA, Bagshaw RD, Hubner NC, Al-Hakim A, Bouchard A, Faubert D, Fermin D, Dunham WH, Goudreault M, Lin ZY, Badillo BG, Pawson T, Durocher D, Coulombe B, Aebersold R, Superti-Furga G, Colinge J, Heck AJR, Choi H, Gstaiger M, Mohammed S, Cristea IM, Bennett KL, Washburn MP, Raught B, Ewing RM, Gingras AC, Nesvizhskii AI. Nat Methods 2013; 10(8): 730-736.

Affinity purification coupled with mass spectrometry (AP-MS) is a widely used approach for the identification of protein-protein interactions. However, for any given protein of interest, determining which of the identified polypeptides represent bona fide interactors versus those that are background contaminants (for example, proteins that interact with the solid-phase support, affinity reagent or epitope tag) is a challenging task. The standard approach is to identify nonspecific interactions using one or more negative-control purifications, but many small-scale AP-MS studies do not capture a complete, accurate background protein set when available controls are limited. Fortunately, negative controls are largely bait independent. Hence,

aggregating negative controls from multiple AP-MS studies can increase coverage and improve the characterization of background associated with a given experimental protocol. Here the authors present the contaminant repository for affinity purification (the CRAPome) and describe its use for scoring protein-protein interactions. The repository (currently available for Homo sapiens and Saccharomyces cerevisiae) and computational tools are freely accessible at http://www.crapome.org/.

A Database Of Caenorhabditis Elegans Behavioral Phenotypes. Yemini E, Jucikas T, Grundy LJ, Brown AEX, Schafer WR. Nat Methods 2013; 10(9): 877-879.
Using low-cost automated tracking microscopes, the authors have generated a behavioral database for 305 *Caenorhabditis elegans* strains, including 76 mutants with no previously described phenotype. The growing database currently consists of 9,203 short videos segmented to extract behavior and morphology features, and these videos and feature data are available online for further analysis. The database also includes summary statistics for 702 measures with statistical comparisons to wild-type controls so that phenotypes can be identified and understood by users.

Recombinant Antibodies To Histone Post-Translational Modifications. Hattori T, Taft JM, Swist KM, Luo H, Witt H, Slattery M, Koide A, Ruthenburg AJ, Krajewski K, Strahl BD, White KP, Farnham PJ, Zhao Y, Koide S. Nat Methods 2013; 10(10): 992-995.
Variability in the quality of antibodies to histone post-translational modifications (PTMs) is a widely recognized hindrance in epigenetics research. Here, the authors produced recombinant antibodies to the trimethylated lysine residues of histone H3 with high specificity and affinity and no lot-to-lot variation. These recombinant antibodies performed well in common epigenetics applications, and enabled us to identify positive and negative correlations among histone PTMs.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

White Matter Characterization of Adolescent Binge Drinking with and without Co-occurring Marijuana Use: A 3-year Investigation. Jacobus J, Squeglia LM, Bava S, Tapert SF. Psychiatry Res. 2013 Dec 30; 214(3): 374-381.
The aims of this study were to investigate the consequences of prolonged patterns of alcohol and marijuana use on white matter integrity and neurocognitive functioning in late adolescence, and examine neurodevelopmental trajectories over three years of regular follow-up visits. Three groups of demographically similar teens received assessments every 1.5 years (controls with consistently minimal substance use, n=16; teens who gradually increase their heavy episodic drinking n=17, and continuous binge drinkers with heavy marijuana use, n=21), including comprehensive neuropsychological evaluations, diffusion tensor imaging, and detailed substance use interviews. One-way ANOVA identified fifteen white matter clusters that significantly differed between groups at 3-year follow-up, ages 19-22; controls consistently demonstrated higher values of tissue integrity across fiber tracts. Repeated measures ANOVA revealed significant declines in white matter integrity from baseline to 3-year follow-up in the subsample of substance users, along with poorer global neurocognitive performance in alcohol users with heavy marijuana use by the 18-month follow-up. Findings suggest healthier brain white matter microstructure and better neurocognitive performance for teens free from heavy alcohol and marijuana use. Long-term engagement in these substances may adversely influence white matter and increase vulnerability for development of neuropathology purported to underlie future risk-taking and addictive behaviors.

White Matter Microstructure Abnormalities and Executive Function in Adolescents with Prenatal Cocaine Exposure. Lebel C, Warner T, Colby J, Soderberg L, Roussotte F, Behnke M, Davis Eyler F, Sowell ER. Psychiatry Res. 2013 Aug 30; 213(2): 161-168.
Children with prenatal exposure to cocaine are at higher risk for negative behavioral function and attention difficulties, and have demonstrated brain diffusion abnormalities in frontal white matter regions. However, brain regions beyond frontal and callosal areas have not been investigated using diffusion tensor imaging (DTI). DTI data were collected on 42 youth aged 14-16 years; subjects were divided into three groups based on detailed exposure histories: those with prenatal exposure to cocaine but not alcohol (prenatal cocaine exposure (PCE), n=12), prenatal exposure to cocaine and alcohol (cocaine and alcohol exposure (CAE), n=17), and controls (n=13). Tractography was performed and along-tract diffusion parameters were examined for group differences and correlations with executive function measures. In the right arcuate fasciculus and cingulum, the CAE group had higher fractional anisotropy (FA) and/or lower mean diffusivity (MD) than the other two groups. The PCE group demonstrated lower FA in the right arcuate and higher MD in the splenium of the corpus callosum than controls. Diffusion parameters in tracts with group differences correlated with measures of executive function. In conclusion, these diffusion differences in adolescents with prenatal cocaine exposure suggest localized, long-term structural brain alterations that may underlie attention and response-inhibition difficulties.

The NIH Toolbox Cognition Battery: Results from a Large Normative Developmental Sample (PING). Akshoomoff N, Newman E, Thompson WK, McCabe C, Bloss CS, Chang L, Amaral DG, Casey BJ, Ernst TM, Frazier JA, Gruen JR, Kaufmann WE, Kenet T, Kennedy DN, Libiger O, Mostofsky S, Murray SS, Sowell ER, Schork N, Dale AM, Jernigan TL. Neuropsychology. 2013 Nov 11. [Epub ahead of print].
The NIH Toolbox Cognition Battery (NTCB) was designed to provide a brief, efficient computerized test of key neuropsychological functions appropriate for use in children as young as 3 years of age. This report describes the performance of a large group of typically developing children and adolescents and examines the impact of age and sociocultural variables on test performance. The NTCB was administered to a sample of 1,020 typically developing males and females ranging in age from 3 to 20 years, diverse in terms of socioeconomic status (SES) and race/ethnicity, as part of the new publicly accessible Pediatric Imaging, Neurocognition, and Genetics (PING) data resource, at 9 sites across the United States. General additive models of nonlinear age-functions were estimated from age-differences in test performance on the 8 NTCB subtests while controlling for family SES and genetic ancestry factors (GAFs). Age accounted for the majority of the variance across all NTCB scores, with additional significant contributions of gender on some measures, and of SES and race/ethnicity (GAFs) on all. After adjusting for age and gender, SES and GAFs explained a substantial proportion of the remaining unexplained variance in Picture Vocabulary scores. The results highlight the sensitivity to developmental effects and efficiency of this new computerized assessment battery for neurodevelopmental research. Limitations are observed in the form of some ceiling effects in older children, some floor effects, particularly on executive function tests in the youngest participants, and evidence for variable measurement sensitivity to cultural/socioeconomic factors.

Do Dopamine Gene Variants and Prenatal Smoking Interactively Predict Youth Externalizing Behavior? O'Brien TC, Mustanski BS, Skol A, Cook EH Jr, Wakschlag LS. Neurotoxicol Teratol. 2013 Nov-Dec; 40: 67-73.
Externalizing behaviors (encompassing antisocial, impulsive, and substance use behaviors) are pervasive and impairing across a multitude of settings and developmental contexts. These behaviors, though often investigated separately, are highly comorbid. Prenatal tobacco exposure in interaction with various genetic influences has predicted later externalizing behavior, and recent evidence supports investigating sex differences in these patterns. In the current study, the authors extend this work by (a) examining two functional genetic markers in the dopamine system: the transporter gene (DAT1) and the dopamine receptor D4 gene (DRD4) in interaction with prenatal tobacco exposure to predict a latent composite of externalizing behavior and (b) testing whether these patterns differ by sex of youth in a community sample of adolescents (n=176). The relatively small sample is partially offset by high quality, multi-method prospective measurement. The authors assessed prenatal tobacco exposure using prospective repeated cotinine-corrected reports and externalizing behaviors were assessed utilizing multiple measures across three waves. The interaction between DAT1 (but not DRD4) and prenatal tobacco exposure was statistically significant in boys, and patterns appeared to differ by sex. Risk for externalizing behaviors for exposed boys increased linearly as a function of the 10r DAT1 allele. For exposed girls, there was a trend such that DAT1 heterozygotes had a marginally higher risk than homozygotes. This pattern was not explained by passive gene-environment correlation. Elucidating sex-specific pathways through which early adverse exposures and genetic

susceptibilities contribute to externalizing behavior can inform early targeted prevention efforts for those children at highest risk.

Associations between Children's Socioeconomic Status and Prefrontal Cortical Thickness. Lawson GM, Duda JT, Avants BB, Wu J, Farah MJ. Dev Sci. 2013 Sep; 16(5): 641-652.
Childhood socioeconomic status (SES) predicts executive function performance and measures of prefrontal cortical function, but little is known about its anatomical correlates. Structural MRI and demographic data from a sample of 283 healthy children from the NIH MRI Study of Normal Brain Development were used to investigate the relationship between SES and prefrontal cortical thickness. Specifically, the authors assessed the association between two principal measures of childhood SES, family income and parental education, and gray matter thickness in specific subregions of prefrontal cortex and on the asymmetry of these areas. After correcting for multiple comparisons and controlling for potentially confounding variables, parental education significantly predicted cortical thickness in the right anterior cingulate gyrus and left superior frontal gyrus. These results suggest that brain structure in frontal regions may provide a meaningful link between SES and cognitive function among healthy, typically developing children.

Worth the Wait: Effects of Age of Onset of Marijuana Use on White Matter and Impulsivity. Gruber SA, Dahlgren MK, Sagar KA, Gönenç A, Lukas SE. Psychopharmacology (Berl). 2013 Nov 5. [Epub ahead of print].
Marijuana (MJ) use continues to rise, and as the perceived risk of using MJ approaches an all-time historic low, initiation of MJ use is occurring at even younger ages. As adolescence is a critical period of neuromaturation, teens and emerging adults are at greater risk for experiencing the negative effects of MJ on the brain. In particular, MJ use has been shown to be associated with alterations in frontal white matter microstructure, which may be related to reports of increased levels of impulsivity in this population. The aim of this study was to examine the relationship between age of onset of MJ use, white matter microstructure, and reported impulsivity in chronic, heavy MJ smokers. Twenty-five MJ smokers and 18 healthy controls underwent diffusion tensor imaging and completed the Barratt Impulsiveness Scale. MJ smokers were also divided into early onset (regular use prior to age 16) and late onset (age 16 or later) groups in order to clarify the impact of age of onset of MJ use on these variables. MJ smokers exhibited significantly reduced fractional anisotropy (FA) relative to controls, as well as higher levels of impulsivity. Earlier MJ onset was also associated with lower levels of FA. Interestingly, within the early onset group, higher impulsivity scores were correlated with lower FA, a relationship that was not observed in the late onset smokers. MJ use is associated with white matter development and reported impulsivity, particularly in early onset smokers.

Effects of Prenatal Cocaine/Polydrug Exposure on Substance Use by Age 15. Minnes S, Singer L, Min MO, Wu M, Lang A, Yoon S. Drug Alcohol Depend. 2013 Oct 9. [Epub ahead of print].
This study examined effects of prenatal cocaine exposure (PCE) on tobacco, alcohol, marijuana and cocaine use by age 15. Adolescent (n=358; 183 PCE, 175 non-prenatally cocaine exposed; NCE) drug use was assessed using urine, hair, and/or blood spot samples and self-report (Youth Risk Behavior Surveillance System; YRBSS) at ages 12 and 15. Logistic regression assessed effects of PCE on drug use controlling for other drug exposures, environment and blood lead

levels (BLL). Adjusted percentages of drug use (PCE vs. NCE) were: tobacco 35% vs. 26% (p<.04), marijuana 33% vs. 23% (p<.04), alcohol 40% vs. 35% (p<.01), and any drugs 59% vs. 50% (p<.005). PCE adolescents were twice as likely to use tobacco (OR=2.02, 95% CI=1.05-3.90, p<.04), 2.2 times more likely to use alcohol (OR=2.16, 95% CI=1.21-3.87, p<.01) and 1.8 times more likely to use marijuana (OR=1.81, 95% CI=1.02-3.22, p<.04) than NCE adolescents. A race-by-cocaine-exposure interaction (p<.01) indicated PCE non-African American adolescents had greater probability of tobacco use (65%) than NCE non-African American youth (21%). PCE was associated with any drug use (OR=2.16, CI=1.26-3.69, p<.005), while higher BLL predicted alcohol use (p<.001). Violence exposure was a predictor of tobacco (p<.002), marijuana (p<.0007) and any drug (p<.04). PCE and exposure to violence increased the likelihood of tobacco, marijuana or any drug use by age 15, while PCE and higher early BLL predicted alcohol use. Prevention efforts should target high risk groups prior to substance use initiation.

Patterns of Brain Activation in Foster Children and Nonmaltreated Children during an Inhibitory Control Task. Bruce J, Fisher PA, Graham AM, Moore WE, Peake SJ, Mannering AM. Dev Psychopathol. 2013 Nov; 25(4 Pt 1): 931-941.

Children in foster care have often encountered a range of adverse experiences, including neglectful and/or abusive care and multiple caregiver transitions. Prior research findings suggest that such experiences negatively affect inhibitory control and the underlying neural circuitry. In the current study, event-related functional magnetic resonance imaging was employed during a go/no go task that assesses inhibitory control to compare the behavioral performance and brain activation of foster children and nonmaltreated children. The sample included two groups of 9- to 12-year-old children: 11 maltreated foster children and 11 nonmaltreated children living with their biological parents. There were no significant group differences on behavioral performance on the task. In contrast, patterns of brain activation differed by group. The nonmaltreated children demonstrated stronger activation than did the foster children across several regions, including the right anterior cingulate cortex, the middle frontal gyrus, and the right lingual gyrus, during correct no go trials, whereas the foster children displayed stronger activation than the nonmaltreated children in the left inferior parietal lobule and the right superior occipital cortex, including the lingual gyrus and cuneus, during incorrect no go trials. These results provide preliminary evidence that the early adversity experienced by foster children impacts the neural substrates of inhibitory control.

Challenging Expectancies to Prevent Nonmedical Prescription Stimulant Use: A Randomized, Controlled Trial. Looby A, De Young KP, Earleywine M. Drug Alcohol Depend. 2013 Sep 1; 132(1-2): 362-368.

College students continue to report nonmedical prescription stimulant use to enhance alertness and concentration. Despite increasing prevalence of this behavior, techniques for preventing or treating it are lacking. An intervention that focuses on challenging positive consequence-oriented beliefs about prescription stimulants may be efficacious in preventing use. The current study examined the efficacy of a randomized controlled expectancy challenge intervention to prevent nonmedical prescription stimulant use among 96 at-risk, stimulant-naïve college students (i.e., low grade point average, Greek involvement, binge drinking, cannabis use). Forty-seven participants completed a brief expectancy challenge intervention aimed at modifying positive expectancies for prescription stimulants, to consequently deter initiation of use. The remaining

participants received no intervention. The expectancy challenge successfully modified expectancies related to prescription stimulant effects. Nevertheless, this intervention group and a control group showed comparable rates of nonmedical prescription use at 6-month follow-up. However, negative expectancies were significant predictors of reduced odds of future use. A challenge session appears to modify stimulant-related expectancies, which are related to nonmedical prescription stimulant use. Nevertheless, a more potent challenge or booster sessions might be essential for longer-term changes.

Language Outcomes at 12 Years for Children Exposed Prenatally to Cocaine. Lewis BA, Minnes S, Short EJ, Min MO, Wu M, Lang A, Weishampel P, Singer LT. J Speech Lang Hear Res. 2013 Oct; 56(5): 1662-1676.
In this study, the authors aimed to examine the long-term effects of prenatal cocaine exposure (PCE) on the language development of 12-year-old children using a prospective design, controlling for confounding prenatal drug exposure and environmental factors. Children who were exposed to cocaine in utero (PCE; n = 183) and children who were not exposed to cocaine (i.e., no cocaine exposure [NCE]; n = 181) were followed prospectively from birth to 12 years of age and were compared on language subtests of the Test of Language Development-Intermediate, Third Edition (Hammill & Newcomer, 1997), and phonological processing as measured by the Comprehensive Test of Phonological Processing (Wagner & Torgesen, 1999). The authors evaluated the relationship of PCE to language development through a multivariate analysis of covariance and regression analyses while controlling for confounders. Results show that PCE has small effects on specific aspects of language, including syntax and phonological processing. The caregiver variables of lower maternal vocabulary, more psychological symptoms, and a poorer home environment also had consistent effects on language and phonological processing scores. These findings suggest that PCE continues to have small, subtle effects on specific aspects of language at age 12 years. Phonological processing skills were significantly related to the reading outcomes of letter-word identification, reading fluency, and reading comprehension, indicating that PCE also has small but lasting effects on the language skills that are related to later literacy skills.

Exposure to Maternal Pre- and Postnatal Depression and Anxiety Symptoms: Risk for Major Depression, Anxiety Disorders, and Conduct Disorder in Adolescent Offspring.
Glasheen C, Richardson GA, Kim KH, Larkby CA, Swartz HA, Day NL. Dev Psychopathol. 2013 Nov; 25(4 Pt 1):1045-1063.
This study evaluated whether exposure to maternal pre- or postnatal depression or anxiety symptoms predicted psychopathology in adolescent offspring. Growth mixture modeling was used to identify trajectories of pre- and postnatal depression and anxiety symptoms in 577 women of low socioeconomic status selected from a prenatal clinic. Logistic regression models indicated that maternal pre- and postnatal depression trajectory exposure was not associated with offspring major depression, anxiety, or conduct disorder, but exposure to the high depression trajectory was associated with lower anxiety symptoms in males. Exposure to medium and high pre- and postnatal anxiety was associated with the risk of conduct disorder among offspring. Male offspring exposed to medium and high pre- and postnatal anxiety had higher odds of conduct disorder than did males with low exposure levels. Females exposed to medium or high pre- and postnatal anxiety were less likely to meet conduct disorder criteria than were females with lower exposure. To the best of the authors' knowledge, this is the first study to examine the

effect of pre- and postnatal anxiety trajectories on the risk of conduct disorder in offspring. These results suggest new directions for investigating the etiology of conduct disorder with a novel target for intervention.

Default Mode Network Activity in Male Adolescents with Conduct and Substance Use Disorder. Dalwani MS, Tregellas JR, Andrews-Hanna JR, Mikulich-Gilbertson SK, Raymond KM, Banich MT, Crowley TJ, Sakai JT. Drug Alcohol Depend. 2013 Oct 24. [Epub ahead of print].

Adolescents with conduct disorder (CD) and substance use disorders (SUD) experience difficulty evaluating and regulating their behavior in anticipation of future consequences. Given the role of the brain's default mode network (DMN) in self-reflection and future thought, this study investigates whether DMN is altered in adolescents with CD and SUD, relative to controls. Twenty adolescent males with CD and SUD and 20 male controls of similar ages underwent functional magnetic resonance imaging as they completed a risk-taking decision task. The authors used independent component analysis as a data-driven approach to identify the DMN spatial component in individual subjects. DMN activity was then compared between groups. Compared to controls, patients showed reduced activity in superior, medial and middle frontal gyrus (Brodmann area (BA) 10), retrosplenial cortex (BA 30) and lingual gyrus (BA 18), and bilateral middle temporal gryus (BA 21/22) - DMN regions thought to support self-referential evaluation, memory, foresight, and perspective taking. Furthermore, this pattern of reduced activity in patients remained robust after adjusting for the effects of depression and attention-deficit hyperactivity disorder (ADHD). Conversely, when not adjusting for effects of depression and ADHD, patients demonstrated greater DMN activity than controls solely in the cuneus (BA 19). Collectively, these results suggest that comorbid CD and SUD in adolescents is characterized by atypical activity in brain regions thought to play an important role in introspective processing. These functional imbalances in brain networks may provide further insight into the neural underpinnings of conduct and substance use disorders.

The Role of Prenatal Substance Exposure and Early Adversity on Parasympathetic Functioning from 3 to 6 Years of Age. Conradt E, Abar B, Sheinkopf S, Lester B, Lagasse L, Seifer R, Shankaran S, Bada-Ellzey H, Bauer C, Whitaker T, Hinckley M, Hammond J, Higgins R. Dev Psychobiol. 2013 Sep 3. [Epub ahead of print].

The authors employed latent growth curve analysis to examine trajectories of respiratory sinus arrhythmia (RSA) from 3 to 6 years among children with varying levels of prenatal substance exposure and early adversity. Data were drawn from a prospective longitudinal study of prenatal substance exposure that included 1,121 participants. Baseline RSA and RSA reactivity to an attention-demanding task were assessed at 3, 4, 5, and 6 years. Overall, there were significant individual differences in the trajectories of RSA reactivity, but not baseline RSA, across development. Greater levels of prenatal substance exposure, and less exposure to early adversity, were associated with increased RSA reactivity at 3 years, but by 6 years, both were associated with greater RSA reactivity. Prenatal substance exposure had an indirect influence through early adversity on growth in RSA reactivity. Results are in support of and contribute to the framework of allostatic load.

Analogue Study of Peer Influence on Risk-Taking Behavior in Older Adolescents. Reynolds EK, Macpherson L, Schwartz S, Fox NA, Lejuez CW. Prev Sci. 2013 Oct 11. [Epub ahead of print].
This experimental study aimed to examine whether adolescents act in a riskier manner in the presence of peers and whether peer presence alone influences risk behavior or if a direct influence process is necessary. Utilizing a behavioral task assessing risk-taking, 183 older adolescents (18-20 year olds) came to the laboratory alone once and then were randomized to one of three conditions as follows: alone, peers present, and peers encouraging. An interaction was found such that at baseline, there were no significant differences between the three conditions, but at the experimental session, there was a significant increase in risk task scores particularly for the encouraging condition. These findings challenge proposed models of the interaction between peer influence and risk taking by providing evidence that adolescents take more risks when being encouraged by peers, but that the presence of peers on its own does not lead to more risks than when completing the task alone.

A Preliminary Study of Functional Brain Activation among Marijuana Users during Performance of a Virtual Water Maze Task. Sneider JT, Gruber SA, Rogowska J, Silveri MM, Yurgelun-Todd DA. J Addict. 2013; 2013: 461029.
Numerous studies have reported neurocognitive impairments associated with chronic marijuana use. Given that the hippocampus contains a high density of cannabinoid receptors, hippocampal-mediated cognitive functions, including visuospatial memory, may have increased vulnerability to chronic marijuana use. Thus, the current study examined brain activation during the performance of a virtual analogue of the classic Morris water maze task in 10 chronic marijuana (MJ) users compared to 18 non-using (NU) comparison subjects. Imaging data were acquired using blood oxygen-level dependent (BOLD) functional MRI at 3.0 Tesla during retrieval (hidden platform) and motor control (visible platform) conditions. While task performance on learning trials was similar between groups, MJ users demonstrated a deficit in memory retrieval. For BOLD fMRI data, NU subjects exhibited greater activation in the right parahippocampal gyrus and cingulate gyrus compared to the MJ group for the Retrieval - Motor control contrast (NU > MJ). These findings suggest that hypoactivation in MJ users may be due to differences in the efficient utilization of neuronal resources during the retrieval of memory. Given the paucity of data on visuospatial memory function in MJ users, these findings may help elucidate the neurobiological effects of marijuana on brain activation during memory retrieval.

Craving, Cue Reactivity, and Stimulus Control among Early Stage Young Smokers: Effects of Smoking Intensity and Gender. Carpenter MJ, Saladin ME, Larowe SD, McClure EA, Simonian S, Upadhyaya HP, Gray KM. Nicotine Tob Res. 2013 Sep 16. [Epub ahead of print].
Smoking initiation usually begins in adolescence, but how and for whom nicotine dependence emerges during this period is unclear. The cue-reactivity paradigm is well suited to examine one marker of dependence: craving-related stimulus control, that is, the ability of environmental cues to elicit craving to smoke. This study examined the effects of both level of smoking involvement (daily vs. occasional smoking) and gender on reactivity to both smoking and alcohol cues. Young (age range 16-20; 42% female) daily (n = 55) and occasional (n = 52) smokers were exposed to each of three counterbalanced cues: (a) in vivo smoking (e.g., sight, smell, lighting of cigarette), (b) alcohol (e.g., opening, pouring, and smell of preferred beverage), and (c) neutral cue. Daily smokers exhibited higher levels of tonic (i.e., noncue-elicited) craving than did

occasional smokers. Both groups showed significant increases in craving in response to cues (i.e., cue-elicited craving), with little evidence that cue-elicited craving differed between groups. Females were more cue reactive to both the alcohol and smoking cues than males, particularly for the positively reinforced aspects of smoking (i.e., hedonic craving). There were no gender × group interaction effects in response to either the alcohol or the smoking cue. Findings show the presence of cue-elicited craving even among occasional smokers and are consistent with literature demonstrating heightened sensitivity to environmental cues among females. Cue-elicited craving may be one mechanism that contributes to the maintenance of smoking behavior and perhaps to the development of nicotine dependence within early stage smokers.

Disentangling the Effects of Genetic, Prenatal and Parenting Influences on Children's Cortisol Variability. Marceau K, Ram N, Neiderhiser JM, Laurent HK, Shaw DS, Fisher P, Natsuaki MN, Leve LD. Stress. 2013 Nov; 16(6): 607-615.
Developmental plasticity models hypothesize the role of genetic and prenatal environmental influences on the development of the hypothalamic-pituitary-adrenal (HPA) axis and highlight that genes and the prenatal environment may moderate early postnatal environmental influences on HPA functioning. This article examines the interplay of genetic, prenatal and parenting influences across the first 4.5 years of life on a novel index of children's cortisol variability. Repeated measures data were obtained from 134 adoption-linked families, adopted children and both their adoptive parents and birth mothers, who participated in a longitudinal, prospective US domestic adoption study. Genetic and prenatal influences moderated associations between inconsistency in overreactive parenting from child age 9 months to 4.5 years and children's cortisol variability at 4.5 years differently for mothers and fathers. Among children whose birth mothers had high morning cortisol, adoptive fathers' inconsistent overreactive parenting predicted higher cortisol variability, whereas among children with low birth mother morning cortisol adoptive fathers' inconsistent overreactive parenting predicted lower cortisol variability. Among children who experienced high levels of prenatal risk, adoptive mothers' inconsistent overreactive parenting predicted lower cortisol variability and adoptive fathers' inconsistent overreactive parenting predicted higher cortisol variability, whereas among children who experienced low levels of prenatal risk there were no associations between inconsistent overreactive parenting and children's cortisol variability. Findings supported developmental plasticity models and uncovered novel developmental, gene × environment and prenatal × environment influences on children's cortisol functioning.

Maternal Smoking during Pregnancy and Offspring Conduct Problems: Evidence from 3 Independent Genetically Sensitive Research Designs. Gaysina D, Fergusson DM, Leve LD, Horwood J, Reiss D, Shaw DS, Elam KK, Natsuaki MN, Neiderhiser JM, Harold GT. JAMA Psychiatry. 2013 Sep; 70(9): 956-963.
Several studies report an association between maternal smoking during pregnancy and offspring conduct disorder. However, past research evidences difficulty in disaggregating prenatal environmental influences from genetic and postnatal environmental influences. The objective of this study was to examine the relationship between maternal smoking during pregnancy and offspring conduct problems among children reared by genetically related mothers and genetically unrelated mothers. The following 3 studies using distinct but complementary research designs were used: The Christchurch Health and Development Study (a longitudinal cohort study that includes biological and adopted children), the Early Growth and Development Study (a

longitudinal adoption-at-birth study), and the Cardiff IVF (In Vitro Fertilization) Study (an adoption-at-conception study among genetically related families and genetically unrelated families). Maternal smoking during pregnancy was measured as the mean number of cigarettes per day (0, 1-9, or 10) smoked during pregnancy. Possible covariates were controlled for in the analyses, including child sex, birth weight, race/ethnicity, placement age, and breastfeeding, as well as maternal education and maternal age at birth and family breakdown, parenting practices, and family socioeconomic status. Main outcomes and measures collected included:offspring conduct problems (age range, 4-10 years) reported by parents or teachers using the behavior rating scales by Rutter and Conners, the Child Behavior Checklist and the Children's Behavior Questionnaire Short Form, and the Strengths and Difficulties Questionnaire. A significant association between maternal smoking during pregnancy and offspring conduct problems was observed among children reared by genetically related mothers and genetically unrelated mothers. Results from a meta-analysis affirmed this pattern of findings across pooled study samples. Findings across 3 studies using a complement of genetically sensitive research designs suggest that smoking during pregnancy is a prenatal risk factor for offspring conduct problems when controlling for specific perinatal and postnatal confounding factors.

Family History of Alcohol Use Disorders and Neuromaturation: A Functional Connectivity Study with Adolescents. Spadoni AD, Simmons AN, Yang TT, Tapert SF**.** Am J Drug Alcohol Abuse. 2013 Nov; 39(6): 356-364.
A positive family history (FHP) of alcohol use disorders (AUD) is linked to increased risk for personal AUD, but the mechanisms behind this risk are unclear. Previous research suggests that a subtle neurodevelopmental lag in FHP adolescents may contribute to risk for future AUD. Functional magnetic resonance imaging (fMRI) response to a spatial working memory (SWM) task was examined for markers of neuromaturational delay in 85 youth with and without FHP. It was hypothesized that FHP adolescents (n = 24, ages 12-14 years), as compared to matched FHN youth (n = 26, ages 12-14 years), would show less similarity to brain connectivity observed in older adolescents (n = 35, ages 16-20 years) and that statistical comparison of SWM functional connectivity models would differentiate FHN and FHP youth. Structural equation modeling tested the fit of brain response connectivity between FH groups and against the older-adolescent model. Patterns of connectivity were more similar between older adolescent and FHN than FHP adolescents; FHP youth demonstrated higher association between right posterior and left frontal brain regions than FHN and older adolescent youth. Comparison of FH groups indicated a significant difference on the pathway from the right superior parietal lobule to the left middle frontal gyrus. These findings provide additional support for the notion of a neuromaturational lag in FHP youth. Protracted neuromaturation may be a mechanism by which FH increases risk for alcohol dependence, and this less mature neural connectivity pattern may provide a novel endophenotype for identifying youth at risk for drinking problems.

Hyperactivation of the Cognitive Control Network in Cocaine Use Disorders during a Multisensory Stroop Task. Mayer AR, Wilcox CE, Teshiba TM, Ling JM, Yang Z. Drug Alcohol Depend. 2013 Nov 1; 133(1): 235-241.
It has been suggested that individuals with cocaine use disorders (chronic cocaine abusers, CCA) have impairments in cognitive control, which likely contribute to impairments in decision making around drug use and relapse. However, deficits in cognitive control have currently only been studied under conditions of unisensory stimulation, which may not be reflective of more

realistic multisensory drug cues. The current study employed functional magnetic resonance imaging (fMRI) to measure neuronal activity during a multisensory numeric Stroop task. Despite few differences in reaction time, recently abstinent CCA (N=14) exhibited increased activation in prefrontal cortex, striatum and thalamus during cognitive control relative to a group of carefully matched controls (N=16). Importantly, these neuronal differences were relatively robust in classifying patients from controls (approximately 90% accuracy) and evident during conditions of both low (slow stimulus presentation rate) and relatively high (faster stimulus presentation rate) cognitive demand. In addition, CCA also failed to deactivate the default-mode network during high frequency visual trials. In summary, current results indicate compensatory activation within the cognitive control network in recently abstinent CCA to achieve similar levels of behavioral performance.

Cannabis Cue Reactivity and Craving among Never, Infrequent and Heavy Cannabis Users. Henry EA, Kaye JT, Bryan AD, Hutchison KE, Ito TA. Neuropsychopharmacology. 2013 Nov 22. [Epub ahead of print].
Substance cue reactivity is theorized as playing a significant role in addiction processes, promoting compulsive patterns of drug-seeking and drug-taking behavior. However, research extending this phenomenon to cannabis has been limited. To that end, the goal of the current work was to examine the relationship between cannabis cue reactivity and craving in a sample of 353 participants varying in self-reported cannabis use. Participants completed a visual oddball task whereby neutral, exercise, and cannabis cue images were presented, and a neutral auditory oddball task while event-related brain potentials (ERP) were recorded. Consistent with past research, greater cannabis use was associated with greater reactivity to cannabis images as reflected in the P300 component of the ERP, but not to neutral auditory oddball cues. The latter indicates the specificity of cue reactivity differences as a function of substance-related cues and not generalized cue reactivity. Additionally, cannabis cue reactivity was significantly related to self-reported cannabis craving as well as problems associated with cannabis use.

Identifying Childhood Characteristics that Underlie Premorbid Risk for Substance Use Disorders: Socialization and Boldness. Hicks BM, Iacono WG, McGue M. Dev Psychopathol. 2013 Nov 26: 1-17. [Epub ahead of print].
The authors utilized a longitudinal twin study (N = 2,510) to identify the child characteristics present prior to initiation of substance use that best predicted later substance use disorders. Two independent traits accounted for the majority of premorbid risk: socialization (conformity to rules and conventional values) and boldness (sociability and social assurance, stress resilience, and thrill seeking). Low socialization was associated with disruptive behavior disorders, parental externalizing disorders, and environmental adversity and exhibited moderate genetic (0.45) and shared environmental influences (0.30). Boldness was highly heritable (0.71) and associated with less internalizing distress and environmental adversity. In combination, these traits exhibited robust associations with adolescent and young adult substance use disorders (R = .48 and .50, respectively) and incremental prediction over disruptive behavior disorders, parental externalizing disorders, and environmental adversity. The results were replicated in an independent sample. Socialization and boldness offer a novel conceptualization of underlying risk for substance use disorders that has the potential to improve prediction and theory with implications for basic research, prevention, and intervention.

Precursors of Adolescent Substance Use from Early Childhood and Early Adolescence: Testing a Developmental Cascade Model. Sitnick SL, Shaw DS, Hyde LW. Dev Psychopathol. 2013 Sep 13:1-16. [Epub ahead of print].
This study examined developmentally salient risk and protective factors of adolescent substance use assessed during early childhood and early adolescence using a sample of 310 low-income boys. Child problem behavior and proximal family risk and protective factors (i.e., parenting and maternal depression) during early childhood, as well as child and family factors and peer deviant behavior during adolescence, were explored as potential precursors to later substance use during adolescence using structural equation modeling. Results revealed that early childhood risk and protective factors (i.e., child externalizing problems, mothers' depressive symptomatology, and nurturant parenting) were indirectly related to substance use at the age of 17 via risk and protective factors during early and middle adolescence (i.e., parental knowledge and externalizing problems). The implications of these findings for early prevention and intervention are discussed.

Mental Health and Substance Use Disparities among Urban Adolescent Lesbian and Bisexual Girls. Marshal MP, Dermody SS, Shultz ML, Sucato GS, Stepp SD, Chung T, Burton CM, Markovic N, Hipwell AE. J Am Psychiatr Nurses Assoc. 2013 Sep-Oct; 19(5): 271.
Sexual minority girls (SMGs) report large substance use disparities and victimization experiences, yet there is a dearth of research that focuses exclusively on SMGs. The objective of this study was to examine substance use and mental health disparities among SMGs and to determine whether disparities were larger for African American compared with European American girls. Data were used from Wave 11 of the Pittsburgh Girls Study, a multiple-cohort, prospective study of urban girls. Girls for the current analysis were aged 16 to 19 years. Fifty-five percent were African American. One hundred and seventy-three (8.3%) identified as SMGs, and 1,891 identified as heterosexual. Multiple regression analyses controlling for age, race, and parent education were conducted. SMGs reported a robust pattern of large disparities in externalizing, internalizing, and borderline personality disorder symptoms. There was little evidence to suggest disparities were moderated by race. SMGs and their families would benefit from intervention and prevention programs to reduce disparities among this highly vulnerable population.

Cross-sectional Evidence for a Stress-negative Affect Pathway to Substance Use among Sexual Minority Girls. Marshal MP, Burton CM, Chisolm DJ, Sucato GS, Friedman MS. Clin Transl Sci. 2013 Aug; 6(4): 321-322.
Sexual minority girls (SMGs) are four times more likely to engage in substance use than are heterosexual girls. A better understanding of the explanatory mechanisms of this disparity is needed to inform prevention and intervention programs. The goal of this study was to conduct a preliminary test of a "stress-negative affect" pathway by examining gay-related victimization and depression as mediators of substance use among SMGs. Adolescent girls (N = 156, 41% SMGs) were recruited from two urban adolescent medicine clinics to participate in an NIH-funded study of adolescent substance use. The average age was 17.0 years old and 57% were nonwhite. Mediation analyses were conducted in a multiple regression framework using SPSS and a mediation macro utilizing bias-corrected bootstrapping. Four models were estimated to test mediated pathways from sexual orientation to gay-related victimization (Mediator 1), to depression symptoms (Mediator 2), and then to each of four substance use variables: cigarettes,

marijuana, alcohol, and heavy alcohol use. Significant mediated pathways (mediation tests with 95% CIs) were found for cigarette, alcohol and heavy alcohol use outcome variables. Results provide preliminary support for the minority stress hypothesis and the stress-negative affect pathway, and may inform the development of future prevention and intervention programs.

Maternal Oxytocin Response Predicts Mother-to-Infant Gaze. Kim S, Fonagy P, Koos O, Dorsett K, Strathearn L. Brain Res. 2013 Nov 1. [Epub ahead of print].
The neuropeptide oxytocin is importantly implicated in the emergence and maintenance of maternal behavior that forms the basis of the mother-infant bond. However, no research has yet examined the specific association between maternal oxytocin and maternal gaze, a key modality through which the mother makes social contact and engages with her infant. Furthermore, prior oxytocin studies have assessed maternal engagement primarily during episodes free of infant distress, while maternal engagement during infant distress is considered to be uniquely relevant to the formation of secure mother-infant attachment. Two patterns of maternal gaze, maternal gaze toward and gaze shifts away from the infant, were micro-coded while 50 mothers interacted with their 7-month-old infants during a modified still-face procedure. Maternal oxytocin response was defined as a change from baseline in the mother's plasma oxytocin level following interaction with her infant. The mother's oxytocin response was positively associated with the duration of time her gaze was directed toward her infant, while negatively associated with the frequency with which her gaze shifted away from her infant. Importantly, mothers who showed low/average oxytocin response demonstrated a significant decrease in their infant gaze during periods of infant distress, while such change was not observed in mothers with high oxytocin response. The findings underscore the involvement of oxytocin in regulating the mother's responsive engagement with her infant, particularly in times when the infant's need for access to the mother is greatest.

Preliminary Evidence for a Sex-specific Relationship between Amount of Cannabis Use and Neurocognitive Performance in Young Adult Cannabis Users. Crane NA, Schuster RM, Gonzalez R. J Int Neuropsychol Soc. 2013 Oct; 19(9): 1009-1015. Epub 2013 Aug 20.
Accumulating evidence suggests neuropsychological deficits from cannabis use, with a burgeoning area of preclinical research indicating possible sex-differences. However, few studies have examined how cannabis use may differentially impact neurocognition in male and female cannabis users. As such, the authors examined potential sex-differences in associations between amount of cannabis use (across several time frames) and neurocognitive performance among young adult regular cannabis users. Consistent with previous studies, more cannabis use was generally associated with poorer episodic memory and decision-making, but not other measures of inhibitory control. However, patterns of results suggested sex-specific dissociations. In particular, more cannabis use was more consistently associated with poorer episodic memory performance in females than males. Conversely, more cannabis use was associated with poorer decision-making performance for males, but not females. These results provide further evidence for residual cannabis-associated neurocognitive deficits and suggest the importance of examining the impact of cannabis on neurocognition separately for males and females.

Development of Auditory Event-related Potentials in Infants Prenatally Exposed to Methadone. Paul JA, Logan BA, Krishnan R, Heller NA, Morrison DG, Pritham UA, Tisher PW, Troese M, Brown MS, Hayes MJ. Dev Psychobiol. 2013 Sep 6. [Epub ahead of print].
Developmental features of the P2 auditory ERP in a change detection paradigm were examined in infants prenatally exposed to methadone. Opiate dependent pregnant women maintained on methadone replacement therapy were recruited during pregnancy (N = 60). Current and historical alcohol and substance use, SES, and psychiatric status were assessed with a maternal interview during the third trimester. Medical records were used to collect information regarding maternal medications, monthly urinalysis, and breathalyzer to confirm comorbid drug and alcohol exposures. Between birth and 4 months infant ERP change detection performance was evaluated on one occasion with the oddball paradigm (.2 probability oddball) using pure-tone stimuli (standard = 1 kHz and oddball = 2 kHz frequency) at midline electrode sites, Fz, Cz, Pz. Infant groups were examined in the following developmental windows: 4-15, 16-32, or 33-120 days PNA. Older groups showed increased P2 amplitude at Fz and effective change detection performance at P2 not seen in the newborn group. Developmental maturation of amplitude and stimulus discrimination for P2 has been reported in developing infants at all of the ages tested and data reported here in the older infants are consistent with typical development. However, it has been previously reported that the P2 amplitude difference is detectable in neonates; therefore, absence of a difference in P2 amplitude between stimuli in the 4-15 days group may represent impaired ERP performance by neonatal abstinence syndrome or prenatal methadone exposure.

Adolescent Friendships in the Context of Dual Risk: The Roles of Low Adolescent Distress Tolerance and Harsh Parental Response to Adolescent Distress. Ehrlich KB, Cassidy J, Gorka SM, Lejuez CW, Daughters SB. Emotion. 2013 Oct; 13(5): 843-851. 2013 Jun 24.
Given extensive evidence about the importance of relationships with friends during development, a large body of research has examined the correlates of these significant social experiences. Most of this research, however, has examined either individual characteristics (e.g., behavior, personality) or contextual factors (e.g., family), and most of the work has studied relationships during childhood. The present study extended previous research by examining how both an individual factor (adolescent distress tolerance) and a contextual factor (parental response to adolescent distress) are linked to adolescents' friendships. Adolescents (N = 161) completed two behavioral measures of distress tolerance, and parents reported about their responses to adolescent distress. Although distress tolerance and parental responses to distress were not directly associated with adolescents' positive or negative friendship experiences, for adolescents with low distress tolerance, harsh parental responses were negatively associated with adolescents' positive friendship quality. Further, for adolescents whose parents used harsh responses to distress, distress tolerance was negatively associated with adolescents' positive friendship quality. Results highlight the importance of studying both individual and familial factors related to adolescents' social functioning.

Thalamo-cortical Activation and Connectivity during Response Preparation in Adults with Persistent and Remitted ADHD. Clerkin SM, Schulz KP, Berwid OG, Fan J, Newcorn JH, Tang CY, Halperin JM. Am J Psychiatry. 2013 Sep 1; 170(9): 1011-1019.
The neural correlates of stimulus-driven processes, such as response preparation, have been posited to be associated with the onset of attention deficit hyperactivity disorder (ADHD) while being distinct from the neural mechanisms associated with recovery. The authors tested this

hypothesis in adults with remitted and persistent ADHD. Thirty-eight young adults who were diagnosed with combined-type ADHD in childhood (probands) and 32 carefully matched comparison subjects were followed longitudinally and scanned with functional MRI while performing an event-related cued reaction time task. Probands were characterized as individuals with persistent or remitted ADHD. Differences in thalamo-cortical activation and functional connectivity during response preparation between comparison subjects and probands and between individuals with persistent ADHD and those with remitted ADHD were assessed by contrasting neural activation and functional connectivity during cue or noncue events. Probands exhibited less cue-related activation than comparison subjects in the thalamus, anterior cingulate cortex, supplementary motor area, inferior parietal lobe, and dorsolateral prefrontal cortex despite similar overall patterns of activation. There were no differences in activation between individuals in the remitted ADHD group and those in the persistent ADHD group in any hypothesized regions. However, cue-related functional connectivity between the right thalamus and brainstem was greater in comparison subjects relative to probands, and cue-related connectivity was greater between the right thalamus and prefrontal regions in individuals with remitted ADHD relative to those with persistent ADHD. Decreased thalamo-cortical activation during response preparation was present in adults diagnosed with ADHD in childhood regardless of symptom remission in adulthood, and may be partly driven by less functional coordination between the brainstem and thalamus. Greater functional integration of the thalamo-cortical network might parallel symptom recovery.

Early Adolescent Cortical Thinning is Related to Better Neuropsychological Performance. Squeglia LM, Jacobus J, Sorg SF, Jernigan TL, Tapert SF. Brain Res. 2013 Nov 6; 1537: 59-68.
Adolescence is characterized by significant neuromaturation, including extensive cortical thinning, particularly in frontal regions. The goal of this study was to examine the behavioral correlates of neurostructural development in early adolescence. Participants were 185 healthy 12- to 14-year-olds (44% female) recruited from local schools. Participants completed a comprehensive neuropsychological test battery and magnetic resonance imaging session. Cortical surface reconstruction and thickness estimates were performed via FreeSurfer. Age and cortical thickness were negatively correlated in 10 brain regions, 7 of which were in frontal areas ($\beta = -.15$ to $-.25$, $ps \leq .05$). Hierarchical linear regressions examined the influence of cortical thickness on working memory, attention, verbal learning and memory, visuospatial functioning, spatial planning and problem solving, and inhibition, controlling for age and intracranial volume. Thinner parietal cortices predicted better performances on tests of verbal learning and memory, visuospatial functioning, and spatial planning and problem solving ($\beta = -.14$ to $-.24$, $ps \leq .05$). Age, spanning from 12 to 14 years, accounted for up to 6% of cortical thickness, suggesting substantial thinning during early adolescence, with males showing more accelerated thinning than females between ages 12 and 14. For both males and females, thinner parietal association cortices corresponded with better neurocognitive functioning above and beyond age alone.

Affective and Executive Network Processing Associated with Persuasive Antidrug Messages. Ramsay IS, Yzer MC, Luciana M, Vohs KD, MacDonald AW 3rd**.** J Cogn Neurosci. 2013 Jul; 25(7):1136-1147. 2013 Mar 26. [Epub ahead of print].
Previous research has highlighted brain regions associated with socioemotional processes in persuasive message encoding, whereas cognitive models of persuasion suggest that executive brain areas may also be important. The current study aimed to identify lateral prefrontal brain

areas associated with persuasive message viewing and understand how activity in these executive regions might interact with activity in the amygdala and medial pFC. Seventy adolescents were scanned using fMRI while they watched 10 strongly convincing antidrug public service announcements (PSAs), 10 weakly convincing antidrug PSAs, and 10 advertisements (ads) unrelated to drugs. Antidrug PSAs compared with nondrug ads more strongly elicited arousal-related activity in the amygdala and medial pFC. Within antidrug PSAs, those that were prerated as strongly persuasive versus weakly persuasive showed significant differences in arousal-related activity in executive processing areas of the lateral pFC. In support of the notion that persuasiveness involves both affective and executive processes, functional connectivity analyses showed greater coactivation between the lateral pFC and amygdala during PSAs known to be strongly (vs. weakly) convincing. These findings demonstrate that persuasive messages elicit activation in brain regions responsible for both emotional arousal and executive control and represent a crucial step toward a better understanding of the neural processes responsible for persuasion and subsequent behavior change.

Predictors of Methamphetamine Psychosis: History of ADHD-relevant Childhood Behaviors and Drug Exposure. Salo R, Fassbender C, Iosif AM, Ursu S, Leamon MH, Carter C. Psychiatry Res. 2013 Dec 15; 210(2): 529-535 2013. Jul 26. [Epub ahead of print].
The goal of this study was to extend the authors' previous research that reported a significant association between Attention Deficit Hyperactivity Disorder (ADHD)-relevant childhood behaviors and the frequency of methamphetamine (MA)-induced psychotic symptoms in an expanded sample. 190 participants who met DSM-IV criteria for MA dependence were administered the Methamphetamine Experience Questionnaire that assessed MA-induced psychosis. Data related to MA exposure, comorbid drug use, education, familial psychiatric history and assessments of ADHD-relevant childhood behaviors as measured by the Wender Utah Rating Scale (WURS) were collected. Although WURS scores did not differ between 145 MAP+ and 45 MAP- subjects, MAP+ subjects with higher WURS scores were significantly more likely to report more frequent psychosis. Although mean daily MA dosage did not differ between the MAP+ and MAP- subjects, MAP+ subjects who consumed larger doses of MA were significantly more likely to experience frequent psychosis. These data suggest that ADHD-relevant childhood behaviors may interact with MA exposure to reflect a neurobiological vulnerability related to the emergence of frequent MA-induced psychotic symptoms. These results may elucidate factors that contribute to the psychiatric sequelae of MA abuse.

Neural Sensitivity to Absolute and Relative Anticipated Reward in Adolescents. Vaidya JG, Knutson B, O'Leary DS, Block RI, Magnotta V. PLoS One. 2013; 8(3). 2013 Mar 27. [Epub ahead of print].
Adolescence is associated with a dramatic increase in risky and impulsive behaviors that have been attributed to developmental differences in neural processing of rewards. In the present study, the authors sought to identify age differences in anticipation of absolute and relative rewards. To do so, they modified a commonly used monetary incentive delay (MID) task in order to examine brain activity to relative anticipated reward value (neural sensitivity to the value of a reward as a function of other available rewards). This design also made it possible to examine developmental differences in brain activation to absolute anticipated reward magnitude (the degree to which neural activity increases with increasing reward magnitude). While undergoing fMRI, 18 adolescents and 18 adult participants were presented with cues associated

with different reward magnitudes. After the cue, participants responded to a target to win money on that trial. Presentation of cues was blocked such that two reward cues associated with $.20, $1.00, or $5.00 were in play on a given block. Thus, the relative value of the $1.00 reward varied depending on whether it was paired with a smaller or larger reward. Reflecting age differences in neural responses to relative anticipated reward (i.e., reference dependent processing), adults, but not adolescents, demonstrated greater activity to a $1 reward when it was the larger of the two available rewards. Adults also demonstrated a more linear increase in ventral striatal activity as a function of increasing absolute reward magnitude compared to adolescents. Additionally, reduced ventral striatal sensitivity to absolute anticipated reward (i.e., the difference in activity to medium versus small rewards) correlated with higher levels of trait Impulsivity. Thus, ventral striatal activity in anticipation of absolute and relative rewards develops with age. Absolute reward processing is also linked to individual differences in impulsivity.

Age-related Changes in Insula Cortical Thickness and Impulsivity: Significance for Emotional Development and Decision-making. Churchwell JC, Yurgelun-Todd DA. Dev Cogn Neurosci. 2013 Jul 20; 6C: 80-86. [Epub ahead of print].
Insula function has been associated with emotional regulation, adjusting to changing outcomes under risk, reward and loss anticipation, discounting of future rewards, and self-rated impulsivity. The role of the insula in these processes may be fundamentally related to prospective thinking, a trait that increases with age. There is evidence that insular cortical thickness shows age related decreases that parallel age related increases in future orientation and planning. The authors tested the hypothesis that nonplanning decreases with age and that insula thickness is related to both age and nonplanning impulsivity. Fifty-nine male and female participants, ranging in age from 10 to 22 years old, underwent structural magnetic resonance imaging (MRI) procedures and were assessed using the Barratt Impulsiveness Scale (BIS). The authors observed that anterior insula thickness and nonplanning impulsivity show an inverse relationship with age and that there is a significant positive linear relationship between anterior insula thickness and nonplanning.

Neuroeconomics and Adolescent Substance Abuse: Individual Differences in Neural Networks and Delay Discounting. Stanger C, Elton A, Ryan SR, James GA, Budney AJ, Kilts CD. J Am Acad Child Adolesc Psychiatry. 2013 Jul; 52(7): 747-755 2013. Jun 5.
Many adolescents with substance use problems show poor response to evidence-based treatments. Treatment outcome has been associated with individual differences in impulsive decision making as reflected by delay discounting (DD) rates (preference for immediate rewards). Adolescents with higher rates of DD were expected to show greater neural activation in brain regions mediating impulsive/habitual behavioral choices and less activation in regions mediating reflective/executive behavioral choices. Thirty adolescents being treated for substance abuse completed a DD task optimized to balance choices of immediate versus delayed rewards, and a control condition accounted for activation during magnitude valuation. A group independent component analysis on functional magnetic resonance imaging time courses identified neural networks engaged during DD. Network activity was correlated with individual differences in discounting rate. Higher discounting rates were associated with diminished engagement of an executive attention control network involving the dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, inferior parietal cortex, cingulate cortex, and precuneus. Higher discounting rates also were associated with less deactivation in a "bottom-up" reward

valuation network involving the amygdala, hippocampus, insula, and ventromedial prefrontal cortex. These 2 networks were significantly negatively correlated. Results support relations between competing executive and reward valuation neural networks and temporal decision making, an important, potentially modifiable risk factor relevant for the prevention and treatment of adolescent substance abuse.

Risk-taking Behavior among Adolescents with Prenatal Drug Exposure and Extrauterine Environmental Adversity. Lambert BL, Bann CM, Bauer CR, Shankaran S, Bada HS, Lester BM, Whitaker TM, Lagasse LL, Hammond J, Higgins RD. J Dev Behav Pediatr. 2013 Nov-Dec; 34(9): 669-679.
High-risk environments characterized by familial substance use, poverty, inadequate parental monitoring, and violence exposure are associated with an increased propensity for adolescents to engage in risk-taking behaviors (e.g., substance use, sexual behavior, and delinquency). However, additional factors such as drug exposure in utero and deficits in inhibitory control among drug-exposed youth may further influence the likelihood that adolescents in high-risk environments will engage in risk-taking behavior. This study examined the influence of prenatal substance exposure, inhibitory control, and sociodemographic/environmental risk factors on risk-taking behaviors in a large cohort of adolescents with and without prenatal cocaine exposure (PCE). Risk-taking behavior (delinquency, substance use, and sexual activity) was assessed in 963 adolescents (433 cocaine-exposed, 530 nonexposed) at 15 years of age. Prenatal cocaine exposure predicted later arrests and early onset of sexual behavior in controlled analyses. Associations were partially mediated, however, by adolescent inhibitory control problems. PCE was not associated with substance use at this age. In addition, male gender, low parental involvement, and violence exposure were associated with greater odds of engaging in risk-taking behavior across the observed domains. Study findings substantiate concern regarding the association between prenatal substance exposure and related risk factors and the long-term outcomes of exposed youth. Access to the appropriate social, educational, and medical services is essential in preventing and intervening with risk-taking behaviors and the potential consequences (e.g., adverse health outcomes and incarceration), especially among high-risk adolescent youth and their families.

Cross-national Comparison of Prenatal Methamphetamine Exposure on Infant and Early Child Physical Growth: A Natural Experiment. Abar B, Lagasse LL, Wouldes T, Derauf C, Newman E, Shah R, Smith LM, Arria AM, Huestis MA, Dellagrotta S, Dansereau LM, Wilcox T, Neal CR, Lester BM. Prev Sci. 2013 Aug 13. [Epub ahead of print].
The current study seeks to compare the effects of prenatal methamphetamine exposure (PME) on infant and child physical growth between the USA and New Zealand (NZ). This cross-national comparison provides a unique opportunity to examine the potential impact of services provided to drug using mothers on child health. The longitudinal Infant Development, Environment and Lifestyle study of PME from birth to 36 months was conducted in the USA and NZ. The US cohort included 204 children with PME and 212 non-PME matched comparisons (NPME); the NZ cohort included 108 children with PME and 115 NPME matched comparisons. Latent growth curve models were used to examine effects of PME, country of origin, and the country × PME interaction on growth in length/height and weight. In regard to length/height, PME and country of origin were associated with initial length and growth over time. There was also a significant interaction effect, such that children with PME in the USA were shorter at birth than children

with PME in NZ after controlling for other prenatal exposures, infant set, socioeconomic status, and maternal height. In regard to weight, there was only an effect of country of origin. Effects of PME on infant and child growth were shown to differ across countries, with exposed children in NZ faring better than exposed children in the USA. Implications for prevention programs and public policy are discussed.

Neuropsychological Findings in Pediatric Maltreatment: Relationship of PTSD, Dissociative Symptoms, and Abuse/Neglect Indices to Neurocognitive Outcomes. De Bellis MD, Woolley DP, Hooper SR. Child Maltreat. 2013 Aug; 18(3): 171-183.
Maltreated (n = 38), maltreated + posttraumatic stress disorder (PTSD; n = 60), and control youth (n = 104) underwent comprehensive neuropsychological testing. The two maltreated groups performed significantly lower on IQ, academic achievement, and nearly all of the neurocognitive domains than controls. Maltreated + PTSD performed significantly worse than maltreated youth without PTSD on a task in the visuospatial domain that assessed higher order visuoconstructive abilities. No group differences were evident on the fine motor domain. PTSD diagnosis duration negatively correlated with the visuospatial, and dissociation negatively correlated with the attention domain. Cumulative lifetime maltreatment types experienced negatively correlated with academic achievement. Sexual abuse negatively correlated with language and memory functions after controlling for other maltreatment types. These data support the adverse effects of maltreatment on neuropsychological functions in youth and suggest that all child protective services identified youth should be comprehensively examined for the integrity of their neuropsychological functioning and academic skills, regardless of the presence or absence of mental health symptoms

Neural Mechanisms of Risky Decision-making and Reward Response in Adolescent Onset Cannabis Use Disorder. De Bellis MD, Wang L, Bergman SR, Yaxley RH, Hooper SR, Huettel SA. Drug Alcohol Depend. 2013 Nov 1; 133(1): 134-145.
Neural mechanisms of decision-making and reward response in adolescent cannabis use disorder (CUD) are underexplored. Three groups of male adolescents were studied: CUD in full remission (n=15); controls with psychopathology without substance use disorder history (n=23); and healthy controls (n=18). The authors investigated neural processing of decision-making and reward under conditions of varying risk and uncertainty with the Decision-Reward Uncertainty Task while participants were scanned using functional magnetic resonance imaging. Abstinent adolescents with CUD compared to controls with psychopathology showed hyperactivation in one cluster that spanned left superior parietal lobule/left lateral occipital cortex/precuneus while making risky decisions that involved uncertainty, and hypoactivation in left orbitofrontal cortex to rewarded outcomes compared to no-reward after making risky decisions. Post hoc region of interest analyses revealed that both control groups significantly differed from the CUD group (but not from each other) during both the decision-making and reward outcome phase of the Decision-Reward Uncertainty Task. In the CUD group, orbitofrontal activations to reward significantly and negatively correlated with total number of individual drug classes the CUD patients experimented with prior to treatment. CUD duration significantly and negatively correlated with orbitofrontal activations to no-reward. The adolescent CUD group demonstrated distinctly different activation patterns during risky decision-making and reward processing (after risky decision-making) compared to both the controls with psychopathology and healthy control groups. These findings suggest that neural differences in risky decision-making and reward

processes are present in adolescent addiction, persist after remission from first CUD treatment, and may contribute to vulnerability for adolescent addiction.

A Genome-wide Association Study of Behavioral Disinhibition. McGue M, Zhang Y, Miller MB, Basu S, Vrieze S, Hicks B, Malone S, Oetting WS, Iacono WG. Behavior Genetics September 2013; 43(5): 363-373.
The authors report results from a genome wide association study (GWAS) of five quantitative indicators of behavioral disinhibition: nicotine, alcohol consumption, alcohol dependence, illicit drugs, and non-substance related behavioral disinhibition. The sample, consisting of 7,188 Caucasian individuals clustered in 2,300 nuclear families, was genotyped on over 520,000 SNP markers from Illumina's Human 660W-Quad Array. Analysis of individual SNP associations revealed only one marker-component phenotype association, between rs1868152 and illicit drugs, with a p value below the standard genome-wide threshold of $5 \times 10(-8)$. Because the authors had analyzed five separate phenotypes, they do not consider this single association to be significant. However, they report 13 SNPs that were associated at $p < 10(-5)$ for one phenotype and $p < 10(-3)$ for at least two other phenotypes, which are potential candidates for future investigations of variants associated with general behavioral disinhibition. Biometric analysis of the twin and family data yielded estimates of additive heritability for the component phenotypes ranging from 49 to 70%, GCTA estimates of heritability for the same phenotypes ranged from 8 to 37%. Consequently, even though the common variants genotyped on the GWAS array appear in aggregate to account for a sizable proportion of heritable effects in multiple indicators of behavioral disinhibition, these data suggest that most of the additive heritability remains "missing".

CLINICAL NEUROSCIENCE RESEARCH

Cannabinoid Modulation of Prefrontal-Limbic Activation during Fear Extinction Learning and Recall in Humans. Rabinak CA, Angstadt M, Lyons M, Mori S, Milad MR, Liberzon I, Luan Phan K. Neurobiology of Learning and Memory. 2013. [Epub ahead of print]. (doi:10.1016/j.nlm.2013.09.009).

Pre-extinction administration of Δ(9)-tetrahydrocannibinol (THC) facilitates recall of extinction in healthy humans, and evidence from animal studies suggest that this likely occurs via enhancement of the cannabinoid system within the ventromedial prefrontal cortex (vmPFC) and hippocampus (HIPP), brain structures critical to fear extinction. However, the effect of cannabinoids on the underlying neural circuitry of extinction memory recall in humans has not been demonstrated. The authors conducted a functional magnetic resonance imaging (fMRI) study using a randomized, double-blind, placebo-controlled, between-subjects design (N=14/group) coupled with a standard Pavlovian fear extinction paradigm and an acute pharmacological challenge with oral dronabinol (synthetic THC) in healthy adult volunteers. They examined the effects of THC on vmPFC and HIPP activation when tested for recall of extinction learning 24h after extinction learning. Compared to subjects who received placebo, participants who received THC showed increased vmPFC and HIPP activation to a previously extinguished conditioned stimulus (CS+E) during extinction memory recall. This study provides the first evidence that pre-extinction administration of THC modulates prefrontal-limbic circuits during fear extinction in humans and prompts future investigation to test if cannabinoid agonists can rescue or correct the impaired behavioral and neural function during extinction recall in patients with PTSD. Ultimately, the cannabinoid system may serve as a promising target for innovative intervention strategies (e.g. pharmacological enhancement of exposure-based therapy) in PTSD and other fear learning-related disorders.

CYP2B6 SNPs are Associated with Methadone Dose Required for Effective Treatment of Opioid Addiction. Levran O, Peles E, Hamon S, Randesi M, Adelson M, Kreek MJ. Addiction Biology 2013; 18: 709–716.

Adequate methadone dosing in methadone maintenance treatment (MMT) for opioid addiction is critical for therapeutic success. One of the challenges in dose determination is the inter-individual variability in dose-response. Methadone metabolism is attributed primarily to cytochrome P450 enzymes CYP3A4, CYP2B6 and CYP2D6. The CYP2B6*6 allele [single nucleotide polymorphisms (SNPs) 785A>G (rs2279343) and 516G>T (rs3745274)] was associated with slow methadone metabolism. To explore the effects of CYP2B6*6 allele on methadone dose requirement, it was genotyped in a well-characterized sample of 74 Israeli former heroin addicts in MMT. The sample is primarily of Middle Eastern/European ancestry, based on ancestry informative markers (AIMs). Only patients with no major co-medication that may affect methadone metabolism were included. The stabilizing daily methadone dose in this sample ranges between 13 and 260 mg (mean 140 52 mg). The mean methadone doses required by subjects homozygous for the variant alleles of the CYP2B6 SNPs 785A>G and 516G>T (88, 96 mg, respectively) were significantly lower than those of the heterozygotes (133, 129 mg, respectively) and the non-carriers (150, 151 mg, respectively) (nominal P = 0.012, 0.048, respectively). The results remain significant after controlling for age, sex and the ABCB1 SNP 1236C>T (rs1128503), which was previously shown to be associated with high methadone dose requirement in this population (P = 0.006, 0.030, respectively). An additional 77 CYP2B6,

CYP3A4 and CYP2D6 SNPs were genotyped. Of these, 24 SNPs were polymorphic and none showed significant association with methadone dose. Further studies are necessary to replicate these preliminary findings in additional subjects and other populations.

Endogenous Opioid Function Mediates the Association Between Laboratory-evoked Pain Sensitivity and Morphine Analgesic Responses. Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Kinner E, Schuster E, Passik S, France CR. Pain. 2013 Sep; 154(9): 1856-1864.

Predictors of responsiveness to opioid analgesic medications are not well understood. This study tested whether individual differences in endogenous opioid (EO) function are associated with analgesic responsiveness to morphine. In randomized, counterbalanced order over 3 sessions, 45 chronic low back pain participants and 31 healthy controls received an opioid antagonist (8 mg naloxone), morphine (0.08 mg/kg), or placebo. Participants then engaged in 2 laboratory-evoked pain tasks (ischemic and thermal). Outcomes included pain threshold, pain tolerance, and pain ratings. Indexes of EO function and morphine analgesic responsiveness were derived for each measure as the difference in pain responses between the placebo condition and naloxone or morphine condition, respectively. For all 7 pain measures across the 2 laboratory pain tasks, greater EO function was associated with significantly lower morphine analgesic responsiveness ($P<0.001$-$P=0.02$). Morphine reduced pain responses of low EO individuals to levels similar to those of high EO individuals receiving placebo. Higher placebo condition-evoked pain sensitivity was associated with significantly greater morphine analgesic responsiveness for 5 of 7 pain measures ($P<0.001$-$P=0.02$). These latter associations were significantly mediated by EO function for 4 of these 5 pain outcomes (all P values<0.05). In the laboratory-evoked pain context, opioid analgesic medications may supplement inadequate EO analgesia, with little incremental benefit in those with preexisting high EO function. Implications for personalized medicine are discussed.

Risk-Taking Behavior: Dopamine D2/D3 Receptors, Feedback, and Frontolimbic Activity. Kohno M, Ghahremani DG, Morales AM, Robertson CL, Ishibashi K, Morgan AT, Mandelkern MA, London ED. Cereb Cortex. 2013 Aug 21. [Epub ahead of print. (doi: 10.1093/cercor/bht218).

Decision-making involves frontolimbic and dopaminergic brain regions, but how prior choice outcomes, dopamine neurotransmission, and frontostriatal activity are integrated to affect choices is unclear. The authors tested 60 healthy volunteers using the Balloon Analogue Risk Task (BART) during functional magnetic resonance imaging. In the BART, participants can pump virtual balloons to increase potential monetary reward or cash out to receive accumulated reward; each pump presents greater risk and potential reward (represented by the pump number). In a separate session, the authors measured striatal D2/D3 dopamine receptor binding potential (BPND) with positron emission tomography in 13 of the participants. Losses were followed by fewer risky choices than wins; and during risk-taking after loss, amygdala and hippocampal activation exhibited greater modulation by pump number than after a cash-out event. Striatal D2/D3 BPND was positively related to the modulation of ventral striatal activation when participants decided to cash out and negatively to the number of pumps in the subsequent trial; but negatively related to the modulation of prefrontal cortical activation by pump number when participants took risk, and to overall earnings. These findings provide in vivo evidence for a

potential mechanism by which dopaminergic neurotransmission may modulate risk-taking behavior through an interactive system of frontal and striatal activity.

Association between Nicotine Dependence Severity, BOLD Response to Smoking Cues, and Functional Connectivity. Claus ED, Blaine SK, Filbey FM, Mayer AR, Hutchison KE. Neuropsychopharmacology. 2013 Nov; 38(12): 2363-2372.
Enhanced motivational salience towards smoking cues is a consequence of chronic nicotine use, but the degree to which this value increases beyond that of other appetitive cues is unknown. In addition, it is unclear how connectivity between brain regions influences cue reactivity and how cue reactivity and functional connectivity are related to nicotine dependence severity. This study examined neural responses during the presentation of smoking cues and appetitive control cues, as well as functional connectivity in 116 smokers with a range of nicotine dependence severity. Smoking cues elicited greater response above baseline than food cues in orbitofrontal cortex (OFC) and supplementary motor area (SMA) and less deactivation below baseline in middle frontal gyrus, inferior parietal lobe, and middle temporal gyrus. Psychophysiological interaction (PPI) analysis using right OFC as a seed revealed increased connectivity with somatosensory cortex and lateral inferior parietal lobe during smoking cues compared with food cues. Similarly, a PPI analysis using left insula as a seed showed stronger connectivity with somatosensory cortex, right insula, OFC, and striatum. Finally, relationships with nicotine dependence scores showed enhanced response in insula and dorsal anterior cingulate cortex in the smoking vs food comparison, and increased connectivity between insula and circuits involved in motivated behavior. Combined, these results suggest that smokers engage attentional networks and default mode networks involved in self-referential processing to a greater degree during smoking cues. In addition, individuals with greater nicotine dependence severity show increased engagement of sensorimotor and motor preparation circuits, suggesting increased reliance on habitual behavior.

Altered Functional Connectivity of the Insular Cortex Across Prefrontal Networks in Cocaine Addiction. Cisler JM, Elton A, Kennedy AP, Young J, Smitherman S, James GA, Kilts CD. Psychiat Res:Neuroimaging. 2013; 213: 39–46.
Interoception is theorized to be an important process mediating substance use disorders, and the insular cortex is recognized as a core neural region supporting interoception. The purpose of this study was to compare the integration of the insular cortex into prefrontal-related resting-state networks between individuals with cocaine dependence and healthy controls. Participants comprised 41 patients with cocaine dependence and 19 controls who underwent a resting-state 3-T functional magnetic resonance imaging scan. Individuals with cocaine dependence demonstrated altered functional connectivity of the insular cortex, predominantly the right insular cortex, with all eight prefrontal-related resting-state networks identified through Independent Component Analysis(ICA). A conjunction analysis demonstrated that the right insular cortex was the neural region with the highest number of common group differences across the networks. There was no evidence that insular cortex connectivity commonly differed between groups for non-prefrontal-related networks. Further, seed-based functional connectivity analyses extended the network analyses and indicated that cocaine dependence was associated with greater connectivity of the right insula with the dorsomedial prefrontal cortex, inferior frontal gyrus, and bilateral dorsolateral prefrontal cortex. These data support the hypothesis that cocaine dependence is related to altered functional interactions of the insular cortex with prefrontal networks. The results suggest possible neural mechanisms by which the insular cortex

and interoceptive information influence cognitive control and decision-making processes presumably mediated by prefrontal networks in the cocaine dependence process.

Striatal-Insula Circuits in Cocaine Addiction: Implications for Impulsivity and Relapse Risk. McHugh MJ, Demers CH, Braud J, Richard Briggs R, Adinoff B, Stein, EA. Am J Drug Alcohol Abuse. 2013 Nov; 39(6): 424-432.
Dysregulated striatal functioning coupled with executive control deficits arising from abnormal frontal cortical function are considered key mechanisms in the development and maintenance of cocaine addiction. The same features are thought to underlie high trait impulsivity observed in cocaine-addicted populations. Employing resting state functional connectivity, the current study sought to identify cortico-striatal circuit alterations in cocaine addiction and examine the degree to which circuit connectivity contributes to relapse risk and impulsivity among cocaine-addicted individuals. Whole-brain resting-state functional magnetic resonance imaging connectivity was assessed in 45 cocaine-addicted individuals relative to 22 healthy controls using seed volumes in the left and right caudate, putamen and nucleus accumbens. Cocaine-addicted individuals completed scans in the final week of a 2–4 weeks residential treatment episode. Relapse by day 30 post-discharge served to separate cocaine-addicted individuals into relapse and non-relapse groups. All participants completed the Barratt Impulsivity Scale (BIS-11a). Cocaine-addicted individuals exhibited reduced positive connectivity between the bilateral putamen and posterior insula and right postcentral gyrus. Group differences were primarily driven by reduced connectivity in relapse individuals relative to controls. No relapse versus non-relapse differences emerged. Impulsivity (BIS-11a) was higher in cocaine-addicted participants, an effect that was partially mediated by reduced putamen-posterior insula connectivity in this group. Cocaine addiction, relapse risk and impulsivity were associated with reduced connectivity in putamen-posterior insula/postcentral gyrus circuits implicated in temporal discounting and habitual responding. Findings provide new insight into the neurobiological mechanisms underlying impulsivity and relapse in cocaine addiction.

A Preliminary Investigation of Stroop-related Intrinsic Connectivity in Cocaine Dependence: Associations with Treatment Outcomes. Mitchell MR, Balodis IM, DeVito EE, CLacadie CM, Yeston J, Scheinost D, Constable RT, Carroll KM, Potenza MN. Am J Drug Alcohol Abuse. 2013 Nov; 39(6): 392-402.
Cocaine-dependent individuals demonstrate neural and behavioral differences compared to healthy comparison subjects when performing the Stroop color-word interference test. Stroop measures also relate to treatment outcome for cocaine dependence. Intrinsic connectivity analyses assess the extent to which task-related regional brain activations are related to each other in the absence of defining a priori regions of interest. This study examined 1) the extent to which cocaine-dependent and non-addicted individuals differed on measures of intrinsic connectivity during fMRI Stroop performance; and 2) the relationships between fMRI Stroop intrinsic connectivity and treatment outcome in cocaine dependence. Sixteen treatment-seeking cocaine-dependent patients and matched non-addicted comparison subjects completed an fMRI Stroop task. Between-group differences in intrinsic connectivity were assessed and related to self-reported and urine-toxicology-based cocaine-abstinence measures. Cocaine-dependent patients vs. comparison subjects showed less intrinsic connectivity in cortical and subcortical regions. When adjusting for individual degree of intrinsic connectivity, cocaine-dependent vs. comparison subjects showed relatively greater intrinsic connectivity in the ventral striatum,

putamen, inferior frontal gyrus, anterior insula, thalamus and substantia nigra. Non-mean-adjusted intrinsic-connectivity measures in the midbrain, thalamus, ventral striatum, substantia nigra, insula and hippocampus negatively correlated with measures of cocaine abstinence. The diminished intrinsic connectivity in cocaine-dependent vs. comparison subjects suggests poorer communication across brain regions during cognitive-control processes. In mean-adjusted analyses, the cocaine-dependent group displayed relatively greater Stroop-related connectivity in regions implicated in motivational processes in addictions. The relationships between treatment outcomes and connectivity in the midbrain and basal ganglia suggest that connectivity represents a potential treatment target.

Inattention, Impulsive Action, and Subjective Response to d-Amphetamine. Weafer J, de Wit H. Drug Alcohol Depend. 2013 133: 127-133.
Both impulsivity and sensitivity to the rewarding effects of drugs have long been considered risk factors for drug abuse. There is some preclinical evidence to suggest that the two are related; however, there is little information about how specific behavioral components of impulsivity are related to the acute euphorigenic effects of drugs in humans. The aim of the current study was to examine the degree to which both inattention and impulsive action predicted subjective response to amphetamine. Healthy adults (n = 165) performed the behavioral tasks and rated their subjective response to amphetamine (0, 5, 10, and 20 mg). Inattention was assessed as attention lapses on a simple reaction time task, and impulsive action was measured by stop RT on the stop task. Subjective response to amphetamine was assessed with the Drug Effects Questionnaire (DEQ) and the Profile of Mood States (POMS). Hierarchical linear regression analyses showed significant negative associations between attention lapses and subjective response to amphetamine on DEQ measures. By contrast, stop RT was positively associated with responses on both DEQ and POMS measures. Additionally, a dose-response relationship was observed, such that the strength of these associations increased with higher doses of amphetamine. These findings suggest that inattention is associated with less subjective response to amphetamine. By contrast, the heightened sensitivity to stimulant drug reward observed in individuals high in impulsive action suggests that this might be one mechanism contributing to increased risk for stimulant drug abuse in these individuals.

Prospective Associations between Brain Activation to Cocaine and No-Go Cues and Cocaine Relapse. Prisciandaro JJ, Myrick H, Henderson S, McRae-Clark AL, Brady KT. Drug Alcohol Depend. 2013 July 1; 131(1–2): 44–49.
The ability to predict potential for relapse to substance use following treatment could be very useful in targeting aftercare strategies. Recently, a number of investigators have focused on using neural activity measured by fMRI to predict relapse propensity. The purpose of the present study was to use fMRI to investigate prospective associations between brain reactivity to cocaine and response inhibition cues and relapse to cocaine use. Thirty cocaine-dependent participants with clean cocaine urine drug screens (UDS) completed a baseline fMRI scan, including a cocaine-cue reactivity task and a go no-go response inhibition task. After participating in a brief clinical trial of d-cycloserine for the facilitation of cocaine-cue extinction, they returned for a one-week follow-up UDS. Associations between baseline activation to cocaine and inhibition cues and relapse to cocaine use were explored. Positive cocaine UDS was significantly associated with cocaine-cue activation in the right putamen and insula, as well as bilateral occipital regions. Associations between positive cocaine UDS and activation to no-go cues were concentrated in

the postcentral gyri, a region involved in response execution. Although preliminary, these results suggest that brain imaging may be a useful tool for predicting risk for relapse in cocaine-dependent individuals. Further, larger-scale naturalistic studies are needed to corroborate and extend these findings.

Robust Changes in Reward Circuitry during Reward Loss in Current and Former Cocaine Users during Performance of a Monetary Incentive Delay Task. Patel KT, Stevens MC, Meda SA, Muska C, Thomas AD, Potenza MN, Pearlson GD. Biol Psychiat. 2013 Oct 1; 74(7): 529-537.

Abnormal function in reward circuitry in cocaine addiction could predate drug use as a risk factor, follow drug use as a consequence of substance-induced alterations, or both. The authors used a functional magnetic resonance imaging monetary incentive delay task (MIDT) to investigate reward-loss neural response differences among 42 current cocaine users, 35 former cocaine users, and 47 healthy subjects who also completed psychological measures and tasks related to impulsivity and reward. They found various reward processing-related group differences in several MIDT phases. Across task phases the authors found a control > current user > former user activation pattern, except for loss outcome, where former compared with current cocaine users activated ventral tegmental area more robustly. They also found regional prefrontal activation differences during loss anticipation between cocaine-using groups. Both groups of cocaine users scored higher than control subjects on impulsivity, compulsivity and reward-punishment sensitivity factors. In addition, impulsivity-related factors correlated positively with activation in amygdala and negatively with anterior cingulate activation during loss anticipation. Compared with healthy subjects, both former and current users displayed abnormal brain activation patterns during MIDT performance. Both cocaine groups differed similarly from healthy subjects, but differences between former and current users were localized to the ventral tegmental area during loss outcome and to prefrontal regions during loss anticipation, suggesting that long-term cocaine abstinence does not normalize most reward circuit abnormalities. Elevated impulsivity-related factors that relate to loss processing in current and former users suggest that these tendencies and relationships may pre-exist cocaine addiction.

Alterations in Endogenous Opioid Functional Measures in Chronic Back Pain. Martikainen IK, Peciña M, Love TM, Nuechterlein EB, Cummiford CM, Green CR, Harris RE, Stohler CS, Zubieta JK. J Neurosci. 2013 Sep 11; 33(37): 14729-14737.

The absence of consistent end organ abnormalities in many chronic pain syndromes has led to a search for maladaptive CNS mechanisms that may explain their clinical presentations and course. Here, the authors addressed the role of brain regional μ-opioid receptor-mediated neurotransmission, one of the best recognized mechanisms of pain regulation, in chronic back pain in human subjects. They compared μ-opioid receptor availability in vivo at baseline, during pain expectation, and with moderate levels of sustained pain in 16 patients with chronic nonspecific back pain (CNBP) and in 16 age- and gender-matched healthy control subjects, using the μ-opioid receptor-selective radioligand [(11)C]carfentanil and positron emission tomography. The authors found that CNBP patients showed baseline increases in thalamic μ-opioid receptor availability, contrary to a previously studied sample of patients diagnosed with fibromyalgia. During both pain expectation and sustained pain challenges, CNBP patients showed regional reductions in the capacity to activate this neurotransmitter system compared with their control sample, further associated with clinical pain and affective state ratings. These results demonstrate

heterogeneity in endogenous opioid system functional measures across pain conditions, and alterations in both receptor availability and endogenous opioid function in CNBP that are relevant to the clinical presentation of these patients and the effects of opioid analgesics on μ-opioid receptors.

Are All Placebo Effects Equal? Placebo Pills, Sham Acupuncture, Cue Conditioning and Their Association. Kong J, Spaeth R, Cook A, Kirsch I, Claggett B, Vangel M, Gollub RL, Smoller JW, Kaptchuk TJ. PLoS One. 2013 Jul 31; 8(7): e67485.
Placebo treatments and healing rituals have been used to treat pain throughout history. The present within-subject crossover study examines the variability in individual responses to placebo treatment with verbal suggestion and visual cue conditioning by investigating whether responses to different types of placebo treatment, as well as conditioning responses, correlate with one another. Secondarily, this study also examines whether responses to sham acupuncture correlate with responses to genuine acupuncture. Healthy subjects were recruited to participate in two sequential experiments. Experiment one is a five-session crossover study. In each session, subjects received one of four treatments: placebo pills (described as Tylenol), sham acupuncture, genuine acupuncture, or no treatment rest control condition. Before and after each treatment, paired with a verbal suggestion of positive effect, each subject's pain threshold, pain tolerance, and pain ratings to calibrated heat pain were measured. At least 14 days after completing experiment one, all subjects were invited to participate in experiment two, during which their analgesic responses to conditioned visual cues were tested. Forty-eight healthy subjects completed experiment one, and 45 completed experiment two. The results showed significantly different effects of genuine acupuncture, placebo pill and rest control on pain threshold. There was no significant association between placebo pills, sham acupuncture and cue conditioning effects, indicating that individuals may respond to unique healing rituals in different ways. This outcome suggests that placebo response may be a complex behavioral phenomenon that has properties that comprise a state, rather than a trait characteristic. This could explain the difficulty of detecting a signature for "placebo responders." However, a significant association was found between the genuine and sham acupuncture treatments, implying that the non-specific effects of acupuncture may contribute to the analgesic effect observed in genuine acupuncture analgesia.

Prepulse Inhibition in HIV-Associated Neurocognitive Disorders. Minassian A, Henry BL, Woods SP, Vaida F, Grant I, Geyer MA, Perry W. J Int Neuropsychol Soc. 2013 Jul; 19(6):709-717.
Sensorimotor inhibition, or the ability to filter out excessive or irrelevant information, theoretically supports a variety of higher-level cognitive functions. Impaired inhibition may be associated with increased impulsive and risky behavior in everyday life. Individuals infected with HIV frequently show impairment on tests of neurocognitive function, but sensorimotor inhibition in this population has not been studied and may be a contributor to the profile of HIV-associated neurocognitive disorders (HAND). Thirty-seven HIV-infected individuals (15 with HAND) and 48 non-infected comparison subjects were assessed for prepulse inhibition (PPI), an eyeblink startle paradigm measuring sensorimotor gating. Although HIV status alone was not associated with PPI deficits, HIV-positive participants meeting criteria for HAND showed impaired PPI compared to cognitively intact HIV-positive subjects. In HIV-positive subjects, PPI was correlated with working memory but was not associated with antiretroviral therapy or illness factors. In conclusion, sensorimotor disinhibition in HIV accompanies deficits in higher-order

cognitive functions, although the causal direction of this relationship requires investigation. Subsequent research on the role of sensorimotor gating on decision-making and risk behaviors in HIV may be indicated.

Methylphenidate Remediates Error-preceding Activation of the Default Mode Brain Regions in Cocaine-addicted Individuals. Matuskey D, Luo X, Zhang S, Morgan PT, Abdelghany O, Malison RT, Li CS. Psychiatry Res. 2013 Nov 30; 214(2): 116-121.
Many previous studies suggest the potential of psychostimulants in improving cognitive functioning. The authors' earlier pharmacological brain imaging study showed that intravenous methylphenidate (MPH) improves inhibitory control by altering cortico-striato-thalamic activations in cocaine-dependent (CD) individuals. Here they provide additional evidence for the effects of MPH in restoring cerebral activations during cognitive performance. Ten CD individuals performed a stop signal task (SST) during functional magnetic resonance imaging (fMRI) in two sessions, in which either MPH (0.5mg/kg body weight) or saline was administered intravenously. In the SST, a frequent go signal instructs participants to make a speeded response and a less frequent stop signal instructs them to withhold the response. The authors' previous work described increased activation of the precuneus/posterior cingulate cortex and ventromedial prefrontal cortex-regions of the default mode network (DMN)-before participants committed a stop error in healthy control but not CD individuals (Bednarski et al., 2011). The current results showed that, compared to saline, MPH restored error-preceding activations of DMN regions in CD individuals. The extent of the changes in precuneus activity was correlated with MPH-elicited increase in systolic blood pressure. These findings suggest that the influence of MPH on cerebral activations may extend beyond cognitive control and provide additional evidence warranting future studies to investigate the neural mechanisms and physiological markers of the efficacy of agonist therapy in cocaine dependence.

Marijuana's Dose-Dependent Effects in Daily Marijuana Smokers. Ramesh D, Haney M, Cooper ZD. Exp Clin Psychopharmacol. 2013 Aug; 21(4): 287-293.
Active marijuana produces significant subjective, psychomotor, and physiological effects relative to inactive marijuana, yet demonstrating that these effects are dose-dependent has proven difficult. This within-subject, double-blind study was designed to develop a smoking procedure to obtain a marijuana dose-response function. In four outpatient laboratory sessions, daily marijuana smokers (N = 17 males, 1 female) smoked six 5-s puffs from 3 marijuana cigarettes (2 puffs/cigarette). The number of puffs from active (≥5.5% Δ^9-tetrahydrocannabinol/THC) and inactive (0.0% THC) marijuana varied according to condition (0, 2, 4, or 6 active puffs); active puffs were always smoked before inactive puffs. Subjective, physiological, and performance effects were assessed prior to and at set time points after marijuana administration. Active marijuana dose-dependently increased heart rate and decreased marijuana craving, despite evidence (carbon monoxide expiration, weight of marijuana cigarettes post-smoking) that participants inhaled less of each active marijuana cigarette than inactive cigarettes. Subjective ratings of marijuana "strength," "high," "liking," "good effect," and "take again" were increased by active marijuana compared with inactive marijuana, but these effects were not dose-dependent. Active marijuana also produced modest, non-dose-dependent deficits in attention, psychomotor function, and recall relative to the inactive condition. In summary, although changes in inhalation patterns as a function of marijuana strength likely minimized the difference between dose conditions, dose-dependent differences in marijuana's cardiovascular effects and

ratings of craving were observed, whereas subjective ratings of marijuana effects did not significantly vary as a function of dose.

Reduced Neural Tracking of Prediction Error in Substance-Dependent Individuals. Tanabe J, Reynolds J, Krmpotich T, Claus E, Thompson LL, Du YP, Banich MT. Am J Psychiatry. 2013 Nov 1; 170(11): 1356-1363.
Substance-dependent individuals make poor decisions on the Iowa Gambling Task, a reward-related decision-making task that involves risk and uncertainty. Task performance depends on several factors, including how sensitive individuals are to feedback and how well they learn based on such feedback. A physiological signal that guides decision making based on feedback is prediction error. The authors investigated whether disruptions in the neural systems underlying prediction error processing in substance-dependent individuals could account for decision-making performance on a modified Iowa Gambling Task. Thirty-two substance-dependent individuals and 30 healthy comparison subjects played a modified version of the Iowa Gambling Task during MR scanning. Trial-to-trial behavior and functional MRI (fMRI) blood-oxygen-level-dependent (BOLD) signal were analyzed using a computational model of prediction error based on internal expectancies. The authors investigated how well BOLD signal tracked prediction error in the striatum and the orbitofrontal cortex as well as over the whole brain in patients relative to comparison subjects. Compared with healthy subjects, substance-dependent patients were less sensitive to loss compared with gain, made less consistent choices, and performed worse on the modified Iowa Gambling Task. The ventral striatum and medial orbitofrontal cortex did not track prediction error as strongly in patients as in healthy subjects. Weaker tracking of prediction error in substance-dependent relative to healthy individuals suggests that altered frontal-striatal error learning signals may underlie decision-making impairments in drug abusers. Computational fMRI may help bridge the knowledge gap between physiology and behavior to inform research aimed at substance abuse treatment.

Avoidance-Based Human Pavlovian-to-Instrumental Transfer. Lewis AH, Niznikiewicz MA, Delamater AR, Delgado MR. Eur J Neurosci. 2013 Oct 10. [Epub ahead of print]. (doi: 10.1111/ejn.12377).
The Pavlovian-to-instrumental transfer (PIT) paradigm probes the influence of Pavlovian cues over instrumentally learned behavior. The paradigm has been used extensively to probe basic cognitive and motivational processes in studies of animal learning. More recently, PIT and its underlying neural basis have been extended to investigations in humans. These initial neuroimaging studies of PIT have focused on the influence of appetitively conditioned stimuli on instrumental responses maintained by positive reinforcement, and highlight the involvement of the striatum. In the current study, the authors sought to understand the neural correlates of PIT in an aversive Pavlovian learning situation when instrumental responding was maintained through negative reinforcement. Participants exhibited specific PIT, wherein selective increases in instrumental responding to conditioned stimuli occurred when the stimulus signaled a specific aversive outcome whose omission negatively reinforced the instrumental response. Additionally, a general PIT effect was observed such that when a stimulus was associated with a different aversive outcome than was used to negatively reinforce instrumental behavior, the presence of that stimulus caused a non-selective increase in overall instrumental responding. Both specific and general PIT behavioral effects correlated with increased activation in corticostriatal circuitry, particularly in the striatum, a region involved in cognitive and motivational processes. These

results suggest that avoidance-based PIT utilizes a similar neural mechanism to that seen with PIT in an appetitive context, which has implications for understanding mechanisms of drug-seeking behavior during addiction and relapse.

Motives for Medical Misuse of Prescription Opioids among Adolescents. McCabe SE, West BT, Boyd CJ. J Pain. 2013 Oct; 14(10): 1208-1216.
This study examined the motives for medical misuse of prescription opioids among adolescents and assessed differences in motives by demographic characteristics, substance abuse, and diversion behaviors. A survey was conducted in 2011 to 2012 and the sample consisted of 2,964 adolescents (51% female). Thirteen percent reported past-year medical use of prescription opioids. Among those prescribed opioids in the past year (n = 393), 17.9% reported medical misuse (e.g., using too much, using to get high, or using to increase alcohol or other drug effects). The most prevalent motives for medical misuse were "to relieve pain" (84.2%) and "to get high" (35.1%). Multivariate analyses indicated that the motives differed by race, and that different motives were associated with different substance abuse and diversion behaviors. The odds of past-year substance abuse among medical misusers motivated by non-pain relief were more than 15 times greater than for nonusers (adjusted odds ratio = 15.2, 95% CI = 6.4-36.2, P < .001). No such differences existed between nonusers and appropriate medical users, or between nonusers and medical misusers motivated by pain relief only. These findings improve our understanding of opioid medication misuse among adolescents and indicate the need for enhanced education about appropriate medical use, pain management, and patient communication with prescribers.

Psychopharmacology of Theobromine in Healthy Volunteers. Baggott MJ, Childs E, Hart AB, de Bruin E, Palmer AA, Wilkinson JE, de Wit H. Psychopharmacology (Berl). 2013 Jul;228(1):109-18.
Theobromine, a methylxanthine related to caffeine and present in high levels in cocoa, may contribute to the appeal of chocolate. However, current evidence for this is limited. The authors conducted a within-subjects placebo-controlled study of a wide range of oral theobromine doses (250, 500, and 1,000 mg) using an active control dose of caffeine (200 mg) in 80 healthy participants. Caffeine had the expected effects on mood including feelings of alertness and cardiovascular parameters. Theobromine responses differed according to dose; it showed limited subjective effects at 250 mg and negative mood effects at higher doses. It also dose-dependently increased heart rate. In secondary analyses, the authors also examined individual differences in the drug's effects in relation to genes related to their target receptors, but few associations were detected. This study represents the highest dose of theobromine studied in humans. The authors conclude that theobromine at normal intake ranges may contribute to the positive effects of chocolate, but at higher intakes, effects become negative.

Amphetamine Increases Errors during Episodic Memory Retrieval. Ballard ME, Gallo DA, de Wit H. J Clin Psychopharmacol. 2013 Oct 16. [Epub ahead of print].
Moderate doses of stimulant drugs are known to enhance memory encoding and consolidation, but their effects on memory retrieval have not been explored in depth. In laboratory animals, stimulants seem to improve retrieval of emotional memories, but comparable studies have not been carried out in humans. In the present study, the authors examined the effects of dextroamphetamine (AMP) on retrieval of emotional and unemotional stimuli in healthy young

adults, using doses that enhanced memory formation when administered before encoding in their previous study. During 3 sessions, healthy volunteers (n = 31) received 2 doses of AMP (10 and 20 mg) and placebo in counterbalanced order under double-blind conditions. During each session, they first viewed emotional and unemotional pictures and words in a drug-free state, and then 2 days later their memory was tested, 1 hour after AMP or placebo administration. Dextroamphetamine did not affect the number of emotional or unemotional stimuli remembered, but both doses increased recall intrusions and false recognition. Dextroamphetamine (20 mg) also increased the number of positively rated picture descriptions and words generated during free recall. These data provide the first evidence that therapeutic range doses of stimulant drugs can increase memory retrieval errors. The ability of AMP to positively bias recollection of prior events could contribute to its potential for abuse.

Do People Serve as Cues to Smoke? Conklin CA, Salkeld RP, Perkins KA, Robin N. Nicotine Tob Res. 2013 Dec; 15(12): 2081-2087.
Recent research has identified that the environments in which smoking has previously occurred can alone, in the absence of any explicit smoking stimuli (e.g., cigarettes, lighters), serve as cues that induce robust craving to smoke. The goal of the present study was to determine if people can similarly function as smoking and nonsmoking cues capable of directly affecting smokers' cue-induced craving. Smokers (N = 72) borrowed cameras to take photos of the people in their lives around whom they do and do not smoke ("personal" smoking and nonsmoking people, PS and PN, respectively). Self-report and physiological cue reactivity to those photos were compared with smokers' reactivity to photos of people unknown to them ("standard" smoking and nonsmoking people, SS and SN, respectively). Results suggest that the people around whom smokers regularly smoke (PS) can alone function as cues capable of eliciting patterns of reactivity similar to that evoked by proximal and environment smoking cues, namely, increased craving to smoke, negative affect, and excitement. In contrast, the people around whom smokers do not smoke become associated with not smoking (PN) and serve a potential protective function by reducing craving and increasing calm. This novel investigation and its results have implications for promoting smoking cessation by developing strategies to manage a smoker's social environment.

MDMA Decreases the Effects of Simulated Social Rejection. Frye CG, Wardle MC, Norman GJ, de Wit H. Pharmacol Biochem Behav. 2013 Dec 3. [Epub ahead of print]
3-4-Methylenedioxymethamphetamine (MDMA) increases self-reported positive social feelings and decreases the ability to detect social threat in faces, but its effects on experiences of social acceptance and rejection have not been determined. The authors examined how an acute dose of MDMA affects subjective and autonomic responses to simulated social acceptance and rejection. They predicted that MDMA would decrease subjective responses to rejection. On an exploratory basis, they also examined the effect of MDMA on respiratory sinus arrhythmia (RSA), a measure of parasympathetic cardiac control often thought to index social engagement and emotional regulation. Over three sessions, healthy adult volunteers with previous MDMA experience (N=36) received capsules containing placebo, 0.75 or 1.5mg/kg of MDMA under counter-balanced double-blind conditions. During expected peak drug effect, participants played two rounds of a virtual social simulation task called "Cyberball" during which they experienced acceptance in one round and rejection in the other. During the task the authors also obtained electrocardiograms (ECGs), from which we calculated RSA. After each round, participants

answered questionnaires about their mood and self-esteem. As predicted, MDMA decreased the effect of simulated social rejection on self-reported mood and self-esteem and decreased perceived intensity of rejection, measured as the percent of ball tosses participants reported receiving. Consistent with its sympathomimetic properties, MDMA decreased RSA as compared to placebo. This finding that MDMA decreases perceptions of rejection in simulated social situations extends previous results indicating that MDMA reduces perception of social threat in faces. Together these findings suggest a cognitive mechanism by which MDMA might produce pro-social behavior and feelings and how the drug might function as an adjunct to psychotherapy. These phenomena merit further study in non-simulated social environments.

Personality and the Acute Subjective Effects of d-Amphetamine in Humans. Kirkpatrick MG, Johanson CE, de Wit H. J Psychopharmacol. 2013 Mar; 27(3): 256-264.
There is evidence that subjective responses to psychoactive drugs are related to personality traits. Here, the authors extend previous findings by examining personality measures in relation to acute responses to *d*-amphetamine (AMPH) in a large sample of healthy volunteers. Healthy adults (*n*=286) completed the Multidimensional Personality Questionnaire Brief Form (MPQ-BF) and participated in four sessions during which they received oral AMPH (0, 5, 10, 20 mg), under double-blind conditions. Subjective responses to the drug were measured using the Profile of Mood States, Addiction Research Center Inventory, and Drug Effects Questionnaire. Drug responses were reduced via principal components analysis to three higher-order factors ('Euphoria', 'Arousal', 'Dysphoria'). Participants were rank ordered on selected MPQ-BF scales; the top and bottom third on each trait were compared on the drug response factors. High trait physical fearlessness was significantly associated with greater amphetamine-related Arousal, and high trait reward sensitivity was significantly associated with greater Euphoria. In addition, high trait impulsivity was significantly associated with greater Arousal and Euphoria. These results provide further evidence that individual differences in the subjective effects of AMPH are partially explained by differences in personality, and are consistent with the idea that both personality and responses to stimulants depend upon shared neurochemical systems.

In the Company of Others: Social Factors Alter Acute Alcohol Effects. Kirkpatrick MG, de Wit H. Psychopharmacology (Berl). 2013 Nov; 230(2): 215-226.
Alcohol is usually consumed in social contexts. However, the drug has been studied mainly under socially isolated conditions, and our understanding of how social setting affects response to alcohol is limited. The current study compared the subjective, physiological, and behavioral effects of a moderate dose of alcohol in moderate social drinkers who were tested in either a social or an isolated context and in the presence of others who had or had not consumed alcohol. Healthy men and women were randomly assigned to either a social group tested in pairs (SOC; N = 24), or an isolated group tested individually (ISO; N = 20). They participated in four sessions, in which they received oral alcohol (0.8 g/kg) or placebo on two sessions each, in quasi-randomized order under double-blind conditions. In the SOC condition, the drug conditions of the co-participants were varied systematically: on two sessions, both participants received the same substance (placebo or alcohol) and on the other two sessions one received alcohol while the other received placebo. Cardiovascular measures, breath alcohol levels, and mood were assessed at regular intervals, and measures of social interaction were obtained in the SOC group. Alcohol produced greater effects on certain subjective measures in the SOC condition compared with the ISO condition, including feelings of intoxication and stimulation, but not on other measures such

as feeling sedated or high, or on cardiovascular measures. Within the SOC condition, participants rated themselves as more intoxicated when their partner received alcohol, and paired subjects interacted more when at least one participant received alcohol. The presence of others enhances some of the subjective and behavioral effects of alcohol, especially the presence of another intoxicated individual. This enhancement of alcohol effects may explain, in part, why it is used in a social context.

Negative Mood and Alcohol Problems are Related to Respiratory Dynamics in Young Adults. Lehrer P, Buckman JF, Mun EY, Vaschillo EG, Vaschillo B, Udo T, Nguyen T, Bates ME. Appl Psychophysiol Biofeedback. 2013 Dec; 38(4): 273-283.
This study examined the relationship of negative affect and alcohol use behaviors to baseline respiration and respiratory response to emotional challenge in young adults (N = 138, 48 % women). Thoracic-to-abdominal ratio, respiratory frequency and variability, and minute volume ventilation were measured during a low-demand baseline task, and emotional challenge (viewing emotionally-valenced, emotionally-neutral, and alcohol-related pictures). Negative mood and alcohol problems principal components were generated from self-report measures of negative affect and mood, alcohol use, and use-related problems. The negative mood component was positively related to a thoracic bias when measured throughout the study (including baseline and picture exposure). There was generally greater respiratory activity in response to the picture cues, although not specifically in response to the content (emotional or alcohol-related) of the picture cues. The alcohol problems component was positively associated with respiratory reactivity to picture cues, when baseline breathing patterns were controlled. Self-report arousal data indicated that higher levels of negative mood, but not alcohol problems, were associated with greater arousal ratings overall. However, those with alcohol problems reported greater arousal to alcohol cues, compared to emotionally neutral cues. These results are consistent with theories relating negative affect and mood to breathing patterns as well as the relationship between alcohol problems and negative emotions, suggesting that the use of respiratory interventions may hold promise for treating problems involving negative affect and mood, as well as drinking problems.

Conditioned Preference to a Methamphetamine-Associated Contextual Cue in Humans. Mayo LM, Fraser D, Childs E, Momenan R, Hommer DW, de Wit H, Heilig M. Neuropsychopharmacology. 2013 May; 38(6): 921-929.
Classical conditioning is widely used to study motivational properties of addictive drugs in animals, but has rarely been used in humans. The authors established a procedure suitable for studying the neurobiology and individual determinants of classical conditioning in humans. Healthy volunteers were randomly assigned to four groups that received methamphetamine or placebo in the presence of distinctive environmental cues under paired or unpaired conditions. During each session, subjects performed tasks known to activate the ventral striatum. Tasks were performed in the presence of a distinctive context, consisting of a screen background image of a beach or mountains, accompanied by corresponding sounds. Separate groups of subjects carried out the tasks under high ($35–50) or low ($5–20) reward conditions. Within each of the two reward conditions, one group (paired) received methamphetamine (20 mg, oral) or placebo consistently associated with one of the contexts, while the other (unpaired) received drug or placebo unrelated to context. A fifth group (paired) performed the tasks with contextual cues but in the absence of monetary incentives. Before and after conditioning, participants carried out a

series of forced choice tasks for the contextual cues, and change of preference over time was analyzed. All paired groups showed a significant increase in preference for the drug-associated context, with a linear trend for increase across the levels of reward. Preference was unrelated to subjective drug effects, and did not change in the unpaired group. These data support the translational utility of our conditioning procedure for studies of reward mechanisms in humans.

Using Conditioned Place Preference to Identify Relapse Prevention Medications. Napier TC, Herrold AA, de Wit H.Neurosci Biobehav Rev. 2013 Nov; 37(9 Pt A): 2081-2086. Stimuli, including contexts, which predict the availability or onset of a drug effect, can acquire conditioned incentive motivational properties. These conditioned properties endure after withdrawal, and can promote drug-seeking which may result in relapse. Conditioned place preference (CPP) assesses the associations between drugs and the context in which they are experienced. Here, the authors review the potential utility of CPP procedures in rodents and humans to evaluate medications that target conditioned drug-seeking responses. They discuss the translational potential of the CPP procedure from rodents to humans, and review findings with FDA-approved treatments that support the use of CPP to develop relapse-reduction medications. They also discuss challenges and methodological questions in applying the CPP procedure to this purpose. They argue that an efficient and valid CPP procedure in humans may reduce the burden of full clinical trials with drug-abusing patients that are currently required for testing promising treatments.

Potential Side Effects of Unhealthy Lifestyle Choices and Health Risks on Basal and Reactive Heart Rate Variability in College Drinkers. Udo T, Mun EY, Buckman JF, Vaschillo EG, Vaschillo B, Bates ME. J Stud Alcohol Drugs. 2013 Sep; 74(5): 787-796. Emerging adults often begin making independent lifestyle choices during college, yet the association of these choices with fundamental indicators of health and adaptability is unclear. The present study examined the relationship between health risks and neurocardiac function in college drinkers. Heart rate variability (HRV) was assessed at baseline and in reaction to a paced breathing challenge in 212 college drinkers (53.8% women). Basal HRV served as a general indicator of health. Reactive HRV (during paced breathing) was used as a marker of an individual's adaptability to challenge. The relationship of HRV to alcohol use, cigarette use, exercise, sleep, and body mass index (BMI) was assessed. Greater alcohol use and less exercise were associated with lower basal HRV. BMI was unrelated to basal HRV but was negatively associated with reactive HRV during the breathing challenge. The authors conclude that high levels of alcohol use and lack of exercise are negative correlates of cardiovascular and general health, even in apparently healthy college drinkers. The negative relationship between BMI and reactive HRV suggests that overweight individuals have reduced ability to psychophysiologically adapt to challenges; understanding the temporal course of this relationship is needed. This study highlights the importance of examining HRV at baseline and in response to a challenge to capture the active neurocardiac processes that contribute to health and adaptive responding. The suppressive effects of health risks on HRV are modifiable; thus, HRV may be useful in evaluating the health benefits of lifestyle change and in promoting change behaviors in college drinkers.

Modeling the Effects of Positive and Negative Mood on the Ability to Resist Eating in Obese and Non-Obese individuals. Udo T, Grilo CM, Brownell KD, Weinberger AH, Dileone RJ, McKee SA. Eat Behav. 2013 Jan; 14(1): 40-46.
This pilot study adapted a well-established drug self-administration paradigm to examine the effects of mood induction on the ability to resist high-calorie foods and subsequent food consumption differently in 15 obese individuals (40.0% women, BMI: 35.1±3.70) and 15 non-obese individuals (46.7% women, BMI: 23.0±1.96). Participants completed two laboratory sessions (positive vs. negative mood conditions) consisting of 3-hour food deprivation, followed by mood induction, and a 3-hour ad-lib eating period, where they were asked to choose between favorite high-calorie snacks and monetary reinforcement. Obese individuals were less able to resist eating and increased high-calorie food consumption during the positive mood condition than the negative condition. Non-obese individuals were less able to resist eating during the negative mood condition than the positive condition, but their total consumption was not affected by the mood conditions. In obese individuals, food craving was associated with less ability to resist eating and greater calorie consumption during the negative mood condition. This is the first study to experimentally demonstrate that mood state may increase vulnerability to food consumption by reducing the ability to resist eating. The ability to resist eating may be a novel dimension of eating behaviors that has a significant contribution to understanding mood-eating relationships.

A Preliminary Study on the Effect of Combined Nicotine Replacement Therapy on Alcohol Responses and Alcohol Self-Administration. Udo T, Harrison EL, Shi J, Tetrault J, McKee SA. Am J Addict. 2013 Nov-Dec; 22(6): 590-597.
Limiting alcohol consumption may help prevent alcohol-mediated smoking relapse in heavy drinking smokers. This pilot study examined whether combining a nicotine patch with nicotine nasal spray has stronger attenuating effects on alcohol response and consumption than a nicotine patch alone. Twenty-two non-alcohol dependent heavy drinking smokers completed the double-blind cross-over, placebo-controlled study (21 mg nicotine patch + nicotine or placebo nasal spray). Six hours after 21 mg nicotine patch application, subjective and physiological responses to a priming drink (0.3 g/kg) were assessed, followed by two 1-hr alcohol self-administration periods, with possible consumption of up to 4 drinks per period (each 0.15 g/kg). Nasal spray (1 mg [active] or 0 mg [placebo] per dose) was administered 10 min prior to the priming dose and each self-administration period. Active nasal spray did not increase serum nicotine levels, compared with placebo administration. The number of drinks consumed did not differ by the nasal spray conditions. However, positive subjective responses to the priming drink were lower in the active nasal spray condition than the placebo nasal spray condition. During the self-administration period, urge to drink was also lower in the active spray condition than the placebo condition. The authors conclude that augmenting the nicotine patch with nicotine nasal spray attenuated positive subjective alcohol response and craving and suggests that future studies should investigate whether these findings translate to a clinical setting.

Test-Retest Reliability of Behavioral Measures of Impulsive Choice, Impulsive Action, and Inattention. Weafer J, Baggott MJ, de Wit H. Exp Clin Psychopharmacol. 2013 Oct 7. [Epub ahead of print].

Behavioral measures of impulsivity are widely used in substance abuse research, yet relatively little attention has been devoted to establishing their psychometric properties, especially their reliability over repeated administration. The current study examined the test-retest reliability of a battery of standardized behavioral impulsivity tasks, including measures of impulsive choice (i.e., delay discounting, probability discounting, and the Balloon Analogue Risk Task), impulsive action (i.e., the stop signal task, the go/no-go task, and commission errors on the continuous performance task), and inattention (i.e., attention lapses on a simple reaction time task and omission errors on the continuous performance task). Healthy adults (n = 128) performed the battery on two separate occasions. Reliability estimates for the individual tasks ranged from moderate to high, with Pearson correlations within the specific impulsivity domains as follows: impulsive choice (r range: .76-.89, ps < .001); impulsive action (r range: .65-.73, ps < .001); and inattention (r range: .38-.42, ps < .001). Additionally, the influence of day-to-day fluctuations in mood, as measured by the Profile of Mood States, was assessed in relation to variability in performance on each of the behavioral tasks. Change in performance on the delay discounting task was significantly associated with change in positive mood and arousal. No other behavioral measures were significantly associated with mood. In sum, the current analysis demonstrates that behavioral measures of impulsivity are reliable measures and thus can be confidently used to assess various facets of impulsivity as intermediate phenotypes for drug abuse.

PET Imaging of High-Affinity α4β2 Nicotinic Acetylcholine Receptors in Humans with 18F-AZAN, a Radioligand with Optimal Brain Kinetics. Wong DF, Kuwabara H, Kim J, Brasic JR, Chamroonrat W, Gao Y, Valentine H, Willis W, Mathur A, McCaul ME, Wand G, Gean EG, Dannals RF, Horti AG. J Nucl Med. 2013 Aug; 54(8): 1308-1314.

The authors evaluated (-)-2-(6-[(18)F]fluoro-2,3'-bipyridin-5'-yl)-7-methyl-7-aza-bicyclo[2.2.1]heptane ((18)F-AZAN), a novel radiotracer that binds to α4β2 nicotinic acetylcholine receptors (α4β2-nAChRs) and shows high specific binding and rapid and reversible kinetics in the baboon and human brain. They tested safety tolerability and test-retest reliability (n = 5) and proposed initial quantification of (18)F-AZAN receptors in 3 healthy human subjects who had nicotine exposure and 9 who did not. They also present a receptor blocking study in a nicotine subject dosed with the α4β2-nAChR-selective partial agonist varenicline. Radiation dosimetry PET/CT experiments indicated that most human organs received doses between 0.008 and 0.015 mSv/MBq, with an effective dose of approximately 0.014 mSv/MBq. The tracer rapidly entered the brain, and the peak was reached before 20 min, even for thalamus. Ninety-minute scans were sufficient for (18)F-AZAN to obtain the ratio at equilibrium of specifically bound radioligand to nondisplaceable radioligand in tissue (BPND) using plasma reference graphical analysis, which showed excellent reproducibility of BPND (test-retest variability < 10%) in the nAChR-rich brain regions. Regional plasma reference graphical analysis BP(ND) values exceeded 2 in the midbrain tegmental nuclei, lateral geniculate body, and thalamus for nonsmokers (n = 9) but were less than 1 in the nAChR-poor brain regions. There was a dramatic reduction of (18)F-AZAN brain uptake in smokers and varenicline-treated subjects. (18)F-AZAN is a highly specific, safe, and effective PET radioligand for human subjects that requires only 90 min of PET scanning to estimate high-affinity α4β2-nAChR in the living human brain.

EPIDEMIOLOGY RESEARCH

Genetic and Environmental Influences On the Familial Transmission Of Externalizing Disorders In Adoptive and Twin Offspring. Hicks BM, Foster KT; Iacono WG, McGue M. JAMA Psychiatry. 2013; 70(10): 1076-1083.
Twin-family studies have shown that parent-child resemblance on substance use disorders and antisocial behavior can be accounted for by the transmission of a general liability to a spectrum of externalizing disorders. Most studies, however, include only biological parents and offspring, which confound genetic and environmental transmission effects. The objective of the present study was to examine the familial transmission of externalizing disorders among both adoptive (genetically unrelated) and biological relatives to better distinguish genetic and environmental mechanisms of transmission. This was a family study design wherein each family included the mother, father, and 2 offspring, including monozygotic twin, dizygotic twin, nontwin biological, and adoptive offspring. Structural equation modeling was used to estimate familial transmission effects and their genetic and environmental influences. Participants were recruited from the community and assessed at a university laboratory. Participants comprised a total of 1590 families with biological offspring and 409 families with adoptive offspring. Offspring participants were young adults (mean age, 26.2 years). Main outcomes and measures were symptom counts of conduct disorder, adult antisocial behavior, and alcohol, nicotine, and drug dependence. Results showed there was a medium effect for the transmission of the general externalizing liability for biological parents (r=0.27-0.30) but not for adoptive parents (r=0.03-0.07). In contrast, adoptive siblings exhibited significant similarity on the general externalizing liability (r=0.21). Biometric analyses revealed that the general externalizing liability was highly heritable (a2=0.61) but also exhibited significant shared environmental influences (c2=0.20). The authors conclude that parent-child resemblance for substance use disorders and antisocial behavior is primarily due to the genetic transmission of a general liability to a spectrum of externalizing disorders. Including adoptive siblings revealed a greater role of shared environmental influences on the general externalizing liability than previously detected in twin studies and indicates that sibling rather than parent-child similarity indexes important environmental risk factors for externalizing disorders.

Is the Relationship Between Early-Onset Cannabis Use and Educational Attainment Causal Or Due To Common Liability? Verweij KJH, Huizink AC, Agrawal A, Martin NG, Lynskey MT. Drug Alcohol Depend. 2013;133(2): 580-586.
Several studies have shown that early cannabis use is correlated with poor educational performance including high school drop-out. The predominant explanation for this relationship is that cannabis use causes disengagement from education. Another explanation is that the association between early cannabis use and educational attainment is not causal, but the result of overlapping risk factors that increase the likelihood of both early cannabis use and disengagement from education. These confounding factors could be of genetic and/or environmental origin. Here the authors use data from a large community-based sample of adult twins (N=3337) who completed a comprehensive semi-structured telephone interview. They first apply the classical twin-design to determine whether genetic and/or environmental influences underlie the relationship between early-onset cannabis use (prior to age 18) and early school leaving. Next, with a co-twin control design the authors investigate whether the relationship between the two variables is more likely due to direct causality or overlapping risk factors. They

find a significant phenotypic correlation between early-onset cannabis use and early school leaving (r=0.26), which could be explained by familial influences (of genetic and/or shared environmental origin). The pattern of odds ratios found in the co-twin control design is not consistent with direct causation, but rather suggests that the association is due to shared environmental factors influencing both variables. These findings suggest that the relationship between early-onset cannabis use and school leaving is due to shared environmental risk factors influencing both the risk of early-onset cannabis use and early school leaving.

The Latent Structure and Predictors Of Non-Medical Prescription Drug Use and Prescription Drug Use Disorders: A National Study. Blanco C, Rafful C, Wall MM, Jin CJ, Kerridge B, Schwartz RP. A National Study. Drug Alcohol Depend. 2013; 133(2): 473-479.
Despite growing concerns about non-medical prescription drug use and prescription drug use disorders, whether vulnerability for these conditions is drug-specific or occurs through a shared liability and common risk factors is unknown. Exploratory and confirmatory factor analysis of Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions were used to examine the latent structure of non-medical prescription drug use and prescription drug use disorders. Multiple Indicators Multiple Causes (MIMIC) analysis was used to examine whether the effect of sociodemographic and psychiatric covariates occurred through the latent factor, directly on each drug class or both. A one-factor model described well the structure of both non-medical prescription drug use and prescription drug use disorders. Younger age, being White, having more intense pain or one of several psychiatric disorders increased the risk of non-medical prescription drug use through the latent factor. The same covariates, except for anxiety disorders also significantly increased the risk of prescription drug use disorders through the latent factor. Older age directly increased the risk of non-medical use of sedatives, and alcohol use disorders decreased the risk of non-medical tranquilizer use. No covariates had direct effects on the risk of any prescription drug use disorders beyond their effect through the latent factor. The risk for non-medical prescription drug use and prescription drug use disorders occurs through a shared liability. Treatment, prevention and policy approaches directed at these drugs as a group maybe more effective than those focused on individual classes of drugs.

Probability and Predictors Of Cannabis Use Disorders Relapse: Results Of The National Epidemiologic Survey On Alcohol and Related Conditions (NESARC). Florez-Salamanca L, Secades-Villa R, Budney AJ, Garcia-Rodriguez O, Wang S, Blanco C. Drug Alcohol Depend. 2013; 132 (1-2):127-133.
This study aims to estimate the odds and predictors of Cannabis Use Disorders (CUD) relapse among individuals in remission. Analyses were done on the subsample of individuals with lifetime history of a CUD (abuse or dependence) who were in full remission at baseline (Wave 1) of the National Epidemiological Survey of Alcohol and Related Conditions (NESARC) (n=2350). Univariate logistic regression models and hierarchical logistic regression model were implemented to estimate odds of relapse and identify predictors of relapse at 3 years follow up (Wave 2). The relapse rate of CUD was 6.63% over an average of 3.6 year follow-up period. In the multivariable model, the odds of relapse were inversely related to time in remission, whereas having a history of conduct disorder or a major depressive disorder after Wave 1 increased the risk of relapse. These findings suggest that maintenance of remission is the most common outcome for individuals in remission from a CUD. Treatment approaches may improve rates of sustained remission of individuals with CUD and conduct disorder or major depressive disorder.

Gender Specific Effect Of Psychological Stress and Cortisol Reactivity On Adolescent Risk Taking. Daughters SB, Gorka SM. Matusiewicz A, Anderson K.. J Abnorm Child Psychol. 2013; 41(5): 749-578.
The purpose of this study was to evaluate how psychological stress, gender and cortisol response to stress relate to risk behavior among 132 14-18year old adolescents. Participants completed a laboratory based risk task prior to and immediately after a computerized psychological stress task, and salivary cortisol was collected from pre-stress to 60min following initial stress exposure. Results indicate that adolescent boys (n=59) and girls (n=73) demonstrate different patterns of risk taking (RT) in response to stress, such that boys evidenced an increase in RT following stress exposure, whereas girls evidenced a decrease in RT. In addition, a gender by cortisol interaction demonstrated that for boys, both a smaller total cortisol output (AUCg) and peak cortisol response to stress (PC) was associated with greater stress-induced RT. Both cortisol measures were unrelated to stress-induced RT among girls. Taken together, data suggest that among boys, a blunted cortisol response to stress underlies an increase in risk taking in the context of psychological stress. Further research with an additional behavioral stress task is needed prior to drawing conclusions regarding the relation between female gender, cortisol response to stress, and risk taking in the context of psychological stress.

Measurement Invariance Of DSM-IV Alcohol, Marijuana and Cocaine Dependence Between Community-Sampled and Clinically Overselected Studies. Derringer J, Krueger RF, Dick DM, Agrawal A, Bucholz KK, Foroud T, Grucza RA, Hesselbrock MN, Hesselbrock V, Kramer J, Nurnberger Jr, JI, Schuckit M, Bierut LJ, Iacono WG, McGue M. Addiction. 2013; 108(10): 1767-1776.
The aim of this study was to examine whether DSM-IV symptoms of substance dependence are psychometrically equivalent between existing community-sampled and clinically overselected studies. A total of 2476 adult twins born in Minnesota and 4121 unrelated adult participants from a case-control study of alcohol dependence served as subjects..Life-time DSM-IV alcohol, marijuana and cocaine dependence symptoms and ever use of each substance were measured. The authors fitted a hierarchical model to the data, in which ever use and dependence symptoms for each substance were indicators of alcohol, marijuana or cocaine dependence which were, in turn, indicators of a multi-substance dependence factor. They then tested the model for measurement invariance across participant groups, defined by study source and participant sex. The hierarchical model fitted well among males and females within each sample [comparative fit index (CFI) > 0.96, Tucker-Lewis index (TLI) > 0.95 and root mean square error of approximation (RMSEA) < 0.04 for all], and a multi-group model demonstrated that model parameters were equivalent across sample- and sex-defined groups (CFI = 0.002 between constrained and unconstrained models). Differences between groups in symptom endorsement rates could be expressed solely as mean differences in the multi-substance dependence factor. Life-time substance dependence symptoms fitted a dimensional model well. Although clinically overselected participants endorsed more dependence symptoms, on average, than community-sampled participants, the pattern of symptom endorsement was similar across groups. From a measurement perspective, DSM-IV criteria are equally appropriate for describing substance dependence across different sampling methods.

Probability and Predictors Of Relapse To Smoking: Results Of The National Epidemiologic Survey On Alcohol and Related Conditions (NESARC). Garcia-Rodriguez O, Secades-Villa R, Florez-Salamanca L, Okuda M, Liu S-M, Blanco C. Drug Alcohol Depend. 2013; 132(3): 479-485.
The goal of this study was to estimate rates of relapse to smoking in the community and to identify predictors of relapse. Data were drawn from the Waves 1 and 2 of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). Logistic regression analyses were used to estimate the probability of relapse at Wave 2 among individuals who were abstinent at Wave 1 given length of abstinence as well as the presence of several sociodemographic, psychopathologic and substance use-related variables at Wave 1. The risk for relapse among individuals who had been abstinent for 12 months or less at the baseline assessment was above 50%. Among individuals who had been abstinent for over a year, risk of relapse decreased hyperbolically as a function of time, and stabilized around 10% after 30 years of abstinence. Although several sociodemo-graphic, psychopathologic and tobacco-related variables predicted relapse in univariate analyses, only younger age at cessation and shorter duration of abstinence independently predicted risk of relapse in multivariable analyses. The first year after a quit attempt constitutes the period of highest risk for relapse. Although the risk for relapse decreases over time, it never fully disappears. Furthermore, younger age at smoking cessation also increases the risk for relapse. This information may help develop more targeted and effective relapse prevention programs.

Risk Factors For Incident Nonmedical Prescription Opioid Use and Abuse and Dependence: Results From A Longitudinal Nationally Representative Sample. Katz C, El-Gabalawy R, Keyes KM, Martins SS, Sareen J. Drug Alcohol Depend. 2013; 132(1-2): 107-113.
There has been a significant increase in opioid prescriptions and the prevalence of opioid nonmedical use. Nonmedical use may lead to opioid abuse/dependence, a serious public health concern. The aim of this paper was to determine the mental and physical health predictors of incident nonmedical prescription opioid use (NMPOU) and abuse/dependence, and the impact of comorbidity in a longitudinal, nationally representative sample.Data come from Waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (N=34,653; 20 years old). Mental disorders were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV edition. Physical conditions were based on self-reports of physician-diagnoses. Multiple logistic regression models examined the associations between mental and physical health predictors at Wave 1 and their association to incident NMPOU and abuse/dependence disorders at Wave 2.After adjusting for sociodemographics, Axis I and II mental disorders and physical conditions, the presence of mental disorders (i.e., mood, personality disorders and substance use disorders), physical conditions (i.e., increasing number of physical conditions, any physical condition, arteriosclerosis or hypertension, cardiovascular disease and arthritis) and sociodemographic factors (i.e., sex and marital status) at Wave 1 positively predicted incident abuse/dependence at Wave 2. Comorbid disorders increased the risk of NMPOU and abuse/dependence. These results suggest the importance of mental and physical comorbidity as a risk for NMPOU and abuse/dependence, emphasizing the need for careful screening practices when prescribing opioids.

Prospective Study Of Substance-Induced and Independent Major Depressive Disorder Among Individuals With Substance Use Disorders In A Nationally Representative Sample. Magidson JF, Wang S, Lejuez CW, Iza M, Blanco C. Depress Anxiety. 2013; 30(6): 538-545.
Depression and substance use disorders (SUDs) commonly co-occur, which presents diagnostic challenges in classifying independent major depressive disorder (MDD) versus substance-induced depressive disorder (SIDD). It remains unclear if distinct characteristics and/or patterns in temporal course distinguish MDD-SUD and SIDD to guide these decisions. Further, evidence suggests that a significant portion of individuals with SIDD are later reclassified as having independent MDD. Continued research to improve our understanding of differences between these two and changes in reclassification over time is necessary for diagnostic clarification and to guide clinical decisions when treating depression in the context of SUDs. The current study compared individuals with MDD-SUD versus SIDD at baseline and examined reclassification of DSM-IV Axis I diagnoses over a 3-year follow up in a large, nationally representative epidemiological sample (n = 2,121). Findings demonstrated that SIDD was extremely rare at both time points. At baseline, individuals with SIDD were more likely to be non-White, have less education, less likely to have insurance, less likely to have dysthymia or alcohol abuse, and more likely to have drug dependence compared to those with independent MDD. Of individuals with SIDD at Wave 1 who had a depressive episode between Waves 1 and 2, the overwhelming majority (>95%) had an independent MDD, not SIDD, episode. There were no significant group differences in the incidence of other mood disorders or SUDs at Wave 2. Findings have important etiological and treatment implications for the classification and treatment of depression in the context of SUDs.

Nicotinic Receptor Gene Variants Interact With Attention Deficient Hyperactive Disorder Symptoms To Predict Smoking Trajectories From Early Adolescence To Adulthood. Lee C-T, Fuemmeler BF, McClernon FJ, Ashley-Koch A, Kollins SH. Addict Behav. 2013; 38(11): 2683-2689.
The aim of this study was to examine the association of single nucleotide polymorphisms (SNPs) of the CHRNB3 (rs13280604) and CHRNA6 (rs892413) nicotinic acetylcholine receptor (nAChR) genes and symptoms of attention deficit hyperactivity disorder (ADHD) in predicting smoking patterns from early adolescence to adulthood. A longitudinal cohort of 1137 unrelated youths from the National Longitudinal Study of Adolescent Health provided responses to four surveys from Waves I to IV, and a genetic sample in Wave III. Growth mixture modeling was used to identify smoking patterns and to assess the effects of the two SNPs and ADHD symptoms on cigarette use over time.There were significant main effects of ADHD symptoms and CHRNA6 variants in predicting the number of cigarettes smoked and the pattern of use over time, respectively. There were no main effects of the CHRNB3 variants. However, a significant CHRNB3 variantADHD symptom interaction was observed, such that individuals with elevated ADHD symptoms and a particular CHRNB3 variant were at increased risk of cigarette use over time. These findings demonstrate that a SNP in a nicotinic receptor gene may interact with ADHD symptoms to link with increased cigarette use across adolescence and young adulthood. Unique associations between specific variants and patterns of ADHD symptoms were identified which may be useful for targeting prevention efforts to individuals at greatest risk for cigarette smoking.

Long-Term Effects Of Laws Governing Youth Access To Tobacco. Grucza RA, Plunk AD, Hipp PR, Cavazos-Rehg P, Krauss MJ, Brownson RC, Bierut LJ. Am J Public Health. 2013; 103(8): 1493-1499.
The authors sought to examine the association between policies governing access to tobacco during adolescence and subsequent adult smoking. They analyzed adult smoking data from the 1998 through 2006-2007 administrations of the US Current Population Survey Tobacco Use Supplement by employing a quasi experimental approach. Participants (n=105,519) were adults, aged 18 to 34 years at the time of the survey. Smoking outcomes included having ever smoked 100 cigarettes, smoking at the time of the survey, and having smoked 10 or more cigarettes a day conditioned on being an ever smoker. These were predicted from exposure to state youth access policies at age 17 years. Four of the 9 policies exhibited significant associations with reduced prevalence of 1 or more smoking outcomes, primarily among women. Lesser effects for other policies could not be ruled out. Restrictions on youth access to tobacco might lead to reduction in smoking prevalence later in adulthood. The effect might be limited to women; the authors estimate that having all policies in place could be associated with a 14% reduction in lifetime smoking prevalence for women, and an additional 29% reduction in heavy smoking among ever smokers.

Seroadaptation In A Sample Of Very Poor Los Angeles Area Men Who Have Sex With Men. Murphy RD, Gorbach PM, Weiss RE, Hucks-Ortiz C, Shoptaw SJ. AIDS Behav. 2013; 17(5): 1862-1872.
Data from 635 very poor men who have sex with men (MSM) were used to identify seroadaptation with 1,102 male partners reported between 2005 and 2007 in Los Angeles as part of the Sexual Acquisition and Transmission of HIV Cooperative Agreement Program. The mean age of the sample was 41.7 years; 53 % had experienced homelessness in the past year. Condoms were reported in 51 % of sexual events involving anal intercourse. HIV seroconcordance was reported in 41 % of sexual partnerships among HIV-positive participants. HIV-positive men were more likely to have oral-only or unprotected receptive anal intercourse and less likely to have unprotected insertive anal intercourse with HIV-negative or unknown partners compared to HIV-positive partners. Even in the face of poverty, HIV-positive MSM report mitigating risks of HIV-transmission though seroadaptation in the context of modest rates of condom use.

Temporal Sequencing Of Nicotine Dependence and Bipolar Disorder In The National Epidemiologic Survey On Alcohol and Related Conditions (NESARC). Martinez-Ortega JM, Goldstein BI, Gutierrez-Rojas L, Sala R, Wang S, Blanco C. J Psychiatr Res. 2013; 47(7): 858-864.
Bipolar disorder (BD) and nicotine dependence (ND) often co-occur. However, the mechanisms underlying this association remain unclear. The authors aimed to examine, for the first time in a national and representative sample, the magnitude and direction of the temporal relationship between BD and ND; and to compare, among individuals with lifetime ND and BD, the sociodemographic and clinical characteristics of individuals whose onset of ND preceded the onset of BD (ND-prior) with those whose onset of ND followed the onset of BD (BD-prior). The sample included individuals with lifetime BD type I or ND (n=7958) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n=43093). Survival analyses and logistic regression models were computed to study the temporal association between ND and BD, and to compare ND-prior (n=135) and BD-prior (n=386) individuals. The

authors found that ND predicted the onset of BD and BD also predicted the onset of ND. Furthermore, the risk of developing one disorder following the other one was greatest early in the course of illness. Most individuals with lifetime ND and BD were BD-prior (72.6%). BD-prior individuals had an earlier onset of BD and a higher number of manic episodes. By contrast, ND-prior individuals had an earlier onset of both daily smoking and ND, and an increased prevalence of alcohol use disorder. In conclusion, ND and BD predict the development of each other. The phenomenology and course of ND and BD varied significantly depending on which disorder had earlier onset.

Modeling the Association Between Sexual Maturation, Transmissible Risk, and Peer Relationships During Childhood and Adolescence On Development Of Substance Use Disorder In Young Adulthood. Horner MS, Tarter R, Kirisci L, Clark DB. Am J Addict. 2013; 22(5): 474-480.

This prospective study investigated pubertal timing and transmissible risk in relation to affiliation with deviant peers on the development of substance use disorder (SUD). Participants were boys (N = 500) ascertained through proband fathers with (N=250), and without (N=250) DSM-III-R lifetime diagnosis of SUD who were prospectively tracked from age 10-12 to 22. Transmissible liability index (TLI), Tanner stage, peer delinquency, and substance use were measured at ages 10-12 and 16. SUD diagnosis during early adulthood was determined. Structural equation modeling revealed two pathways in which transmissible risk and sexual maturation influenced development of SUD. In the first pathway, transmissible risk was correlated with and prospectively predicted affiliation with deviant peers and substance use presaging SUD. In the second pathway, advanced sexual maturation positively predicted affiliation with deviant peers and substance use, which in turn predicted SUD. However, transmissible risk was not associated with pubertal development. These findings indicate that advanced sexual maturation and transmissible risk constitute unrelated facets of SUD liability; however, both factors bias development toward SUD via affiliation with deviant peers. Youth with advanced sexual maturation and/or transmissible risk for SUD are at higher risk for developing SUD. Additional research is needed to determine if addressing these risk factors will contribute to advancements in SUD prevention.

Perceived Likelihood Of Using HIV Pre-Exposure Prophylaxis Medications Among Young Men Who Have Sex With Men. Mustanski B, Johnson AK, Garofalo R, Ryan D, Birkett M. AIDS Behav. 2013; 17(6): 2173-2179.

Pre-exposure prophylaxis (PrEP) is a new strategy for reducing the risk of HIV infection; however, questions about the likelihood of use remain. As part of an ongoing longitudinal study of YMSM, interest in PrEP use under various conditions of side-effects, dosing, and effectiveness were assessed. Participants aged 16-20 living in Chicago and the surrounding areas were recruited beginning December 2009, using a modified form of respondent driven sampling. A cross-sectional sample of 171 HIV negative YMSM interviewed approximately 6 months after initial enrollment was analyzed. This sample was somewhat interested in adopting PrEP as an HIV prevention strategy, particularly if the dosing and side-effects burden was low and the perceived benefits were high. PrEP interest was unrelated with drug use and number of sexual partners, but negatively correlated with number of unprotected anal sex acts. The scale was positively associated with intentions for use in specific risk situations..

Gender Differences In Cannabis Use Disorders: Results From The National Epidemiologic Survey Of Alcohol and Related Conditions. Khan SS, Secades-Villa R, Okuda M, Wang S, Perez-Fuentes G, Kerridge BT, Blanco C. Drug Alcohol Depend. 2013; 130(1-3): 101-108.
The aim of this study was to examine gender differences among individuals diagnosed with DSM-IV lifetime cannabis use disorder (CUD). A nationally representative sample of U.S. adults aged 18 years or older that were diagnosed with lifetime CUD (n=3297): Men (n=2080), Women (n=1217). Data were drawn from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n=43,093). The survey response rate was 81%. Nearly all individuals with CUD had a psychiatric comorbidity (95.6% of men, 94.1% of women). Men with lifetime CUD were more likely than women to be diagnosed with any psychiatric disorder, any substance use disorder and antisocial personality disorder, whereas women with CUD had more mood and anxiety disorders. After adjusting for gender differences in sociodemographic correlates and the prevalence of psychiatric disorders in the general population, women with CUD were at greater risk for externalizing disorders. Men with CUD met more criteria for cannabis abuse, had longer episodes of CUD, smoked more joints, and were older at remission when compared to women with CUD. Women experienced telescoping to CUD. Treatment-seeking rates were very low for both genders, and there were no gender differences in types of services used or reasons for not seeking treatment.There are important gender differences in the clinical characteristics and psychiatric comorbidities among individuals with CUD.

Probability and Predictors Of Treatment-Seeking For Prescription Opioid Use Disorders: A National Study. Blanco C, Iza M, Schwartz RP, Rafful C, Wang S, Olfson M. Drug Alcohol Depend. 2013; 131(1-2): 143-148.
Prescription opioid use disorders are the second most common drug use disorder behind only cannabis use disorders. Despite this, very little is known about the help-seeking behavior among individuals with these disorders. The sample included respondents of the Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) with a lifetime diagnosis of prescription drug use disorders (N=623). Unadjusted and adjusted hazard ratios are presented for time to first treatment-seeking by sociodemographic characteristics and comorbid psychiatric disorders. The lifetime cumulative probability of treatment seeking was 42% and the median delay from prescription drug use disorder onset to first treatment was 3.83 years. Having an earlier onset of prescription opioid use disorder and a history of bipolar disorder, major depression disorder, specific phobia and cluster B personality disorders predicted shorter delays to treatment. Although some comorbid psychiatric disorders increase the rate of treatment-seeking and decrease delays to first-treatment contact rates of treatment-seeking for prescription drug use disorder are low, even when compared with rates of treatment for other substance use disorders. Given the high prevalence and adverse consequences of prescription drug use disorder, there is a need to improve detection and treatment of prescription opioid use disorder.

Personality Dimensions As Common and Broadband-Specific Features For Internalizing and Externalizing Disorders. Hink LK, Rhee SH, Corley RP, Cosgrove VE, Hewitt JK, Schulz-Heik RJ, Lahey BB, Waldman ID. J Abnorm Child Psychol. 2013; 41(6): 939-957.
Several researchers have suggested that the nature of the covariation between internalizing and externalizing disorders may be understood better by examining the associations between temperament or personality and these disorders. The present study examined neuroticism as a potential common feature underlying both internalizing and externalizing disorders and novelty

seeking as a potential broad-band specific feature influencing externalizing disorders alone. Participants were 12- to 18-year-old twin pairs (635 monozygotic twin pairs and 691 dizygotic twin pairs; 48% male and 52% female) recruited from the Colorado Center for Antisocial Drug Dependence. Genetic and nonshared environmental influences shared in common with neuroticism influenced the covariation among distinct internalizing disorders, the covariation among distinct externalizing disorders, and the covariation between internalizing and externalizing disorders. Genetic influences shared in common with novelty seeking influenced the covariation among externalizing disorders and the covariation between major depressive disorder and externalizing disorders, but not the covariation among internalizing disorders or between anxiety disorders and externalizing disorders. Also, after accounting for genetic and environmental influences shared in common with neuroticism and novelty seeking, there were no significant common genetic or environmental influences among the disorders examined, suggesting that the covariance among the disorders is sufficiently explained by neuroticism and novelty seeking. The authors conclude that neuroticism is a heritable common feature of both internalizing disorders and externalizing disorders, and that novelty seeking is a heritable broad-band specific factor that distinguishes anxiety disorders from externalizing disorders.

Trauma Exposure and Posttraumatic Stress Disorder In A National Sample Of Adolescents. McLaughlin KA, Koenen KC, Hill ED, Petukhova M, Sampson NA, Zaslavsky AM, Kessler RC. J Am Acad Child Adolesc Psychiatry. 2013; 52(8): 815-830.e14.
Although exposure to potentially traumatic experiences (PTEs) is common among youths in the United States, information on posttraumatic stress disorder (PTSD) risk associated with PTEs is limited. The authors estimate lifetime prevalence of exposure to PTEs and PTSD, PTE-specific risk of PTSD, and associations of sociodemographics and temporally prior DSM-IV disorders with PTE exposure, PTSD given exposure, and PTSD recovery among U.S. adolescents. Data were drawn from 6,483 adolescent-parent pairs in the National Comorbidity Survey Replication Adolescent Supplement (NCS-A), a national survey of adolescents aged 13 through 17 years. Lifetime exposure to interpersonal violence, accidents/injuries, network/witnessing, and other PTEs was assessed along with DSM-IV PTSD and other distress, fear, behavior, and substance disorders. A majority (61.8%) of adolescents experienced a lifetime PTE. Lifetime prevalence of DSM-IV PTSD was 4.7% and was significantly higher among females (7.3%) than among males (2.2%). Exposure to PTEs, particularly interpersonal violence, was highest among adolescents not living with both biological parents and with pre-existing behavior disorders. Conditional probability of PTSD was highest for PTEs involving interpersonal violence. Predictors of PTSD among PTE-exposed adolescents included female gender, prior PTE exposure, and pre-existing fear and distress disorders. One-third (33.0%) of adolescents with lifetime PTSD continued to meet criteria within 30 days of interview. Poverty, U.S. nativity, bipolar disorder, and PTE exposure occurring after the focal trauma predicted nonrecovery.Interventions designed to prevent PTSD in PTE-exposed youths should be targeted at victims of interpersonal violence with pre-existing fear and distress disorders, whereas interventions designed to reduce PTSD chronicity should attempt to prevent secondary PTE exposure.

The Impact Of Substance Use, Sexual Trauma, and Intimate Partner Violence On Sexual Risk Intervention Outcomes In Couples: A Randomized Trial. Jones DL, Kashy D, Villar-Loubet OM, Cook R, Weiss SM. Ann Behav Med. 2013; 45(3): 318-328.
Few HIV prevention interventions focus on sexual risk reduction as mutual process determined by couple members, though risk behaviors are inter-dependent. This trial examined the impact of substance use, history of sexual trauma, and intimate partner violence on sexual risk associated with participation in a risk reduction intervention. HIV seroconcordant and serodiscordant multicultural couples in Miami, Florida (n=216) were randomized to group (n=112) or individual (n=104) couple-based interventions. Group intervention participants increased condom use in couples in which women had a history of sexual trauma [F(2,221)=3.39, p=0.036] and by partners of alcohol users. History of sexual trauma was a determinant of conflict resolution, predicting negative communication and intimate partner violence. Results emphasize the need for group sexual risk reduction interventions targeting sexual trauma, partner violence, and substance use among HIV seroconcordant and serodiscordant couples.

Longitudinal Associations From Neurobehavioral Disinhibition To Adolescent Risky Sexual Behavior In Boys: Direct and Mediated Effects Through Moderate Alcohol Consumption. Riggs NR, Tate EB, Ridenour TA, Reynolds MD, Zhai ZW, Vanyukov MM, Tarter RE. J Adolesc Health. 2013; 53(4): 465-470.
This longitudinal study tested the hypothesis that neurobehavioral disinhibition (ND) in childhood, mediated by alcohol use, portends risky sexual behavior (number of sexual partners) in midadolescence. Participants were 410 adolescent boys. Neurobehavioral disinhibition was assessed at 11.3 years of age. Frequency and quantity of alcohol use on a typical drinking occasion were assessed at 13.4 years of age at first follow-up, and sexual behavior at 16.0 years at second follow-up. Quantity of alcohol consumed on a typical drinking occasion, but not frequency of alcohol use, mediated the relation between ND and number of sexual partners. These findings indicate that number of sexual partners in midadolescence is predicted by individual differences in boys' psychological self-regulation during childhood and moderate alcohol consumption in early adolescence, and that ND may be a potential target for multi-outcome public health interventions.

Social Support and Recovery Among Mexican Female Sex Workers Who Inject Drugs. Hiller SP, Syvertsen JL, Lozada R, Ojeda VD. J Subst Abuse Treat. 2013; 45(1): 44-54.
This qualitative study describes social support that female sex workers who inject drugs (FSW-IDUs) receive and recovery efforts in the context of relationships with family and intimate partners. The authors conducted thematic analysis of in-depth interviews with 47 FSW-IDUs enrolled in an intervention study to reduce injection/sexual risk behaviors in Tijuana, Mexico. FSW-IDUs received instrumental and emotional social support, which positively and negatively influenced recovery efforts. Participants reported how some intimate partners provided conflicting positive and negative support during recovery attempts. Problematic support (i.e., well-intended support with unintended consequences) occurred in strained family relationships, limiting the positive effects of support. Mexican drug treatment programs should consider addressing social support in recovery curricula through evidence-based interventions that engage intimate partners, children and family to better reflect socio-cultural and contextual determinants of substance abuse.

Individual-and Community-Level Correlates Of Cigarette-Smoking Trajectories From Age 13 To 32 In A U.S. Population-Based Sample. Fuemmeler B, Lee C-T, Ranby KW, Clark T, McClernon FJ, Yang C, Kollins SH. Drug Alcohol Depend. 2013; 132(1-2): 301-308.
Characterizing smoking behavior is important for informing etiologic models and targeting prevention efforts. This study explored the effects of both individual- and community-level variables in predicting cigarette use vs. non-use and level of use among adolescents as they transition into adulthood.Data on 14,779 youths (53% female) were drawn from the National Longitudinal Study of Adolescent Health (Add Health); a nationally representative longitudinal cohort. A cohort sequential design allowed for examining trajectories of smoking typologies from age 13 to 32 years. Smoking trajectories were evaluated by using a zero-inflated Poisson (ZIP) latent growth analysis and latent class growth analysis modeling approach.Significant relationships emerged between both individual- and community-level variables and smoking outcomes. Maternal and peer smoking predicted increases in smoking over development and were associated with a greater likelihood of belonging to any of the four identified smoking groups versus Non-Users. Conduct problems and depressive symptoms during adolescence were related to cigarette use versus non-use. State-level prevalence of adolescent smoking was related to greater cigarette use during adolescence. Individual- and community-level variables that distinguish smoking patterns within the population aid in understanding cigarette use versus non-use and the quantity of cigarette use into adulthood. These findings suggest that efforts to prevent cigarette use would benefit from attention to both parental and peer smoking and individual well-being. Future work is needed to better understand the role of variables in the context of multiple levels (individual and community-level) on smoking trajectories.

Alcohol and Tobacco Use Disorder Comorbidity In Young Adults and the Influence Of Romantic Partner Environments. Meacham MC, Bailey JA, Hill KG, Epstein M, Hawkins JD. Drug Alcohol Depend. 2013; 132(1-2): 149-157.
Although there is considerable evidence that the development of tobacco dependence (TD) and that of alcohol use disorder (AUD) are intertwined, less is known about the comorbid development of these disorders. The present study examines tobacco dependence and alcohol use disorder comorbidity in young adulthood within the context of romantic partner relationships. Data were drawn from the Seattle Social Development Project, a contemporary, ethnically diverse, and gender balanced longitudinal panel including 808 participants. A typological person-centered approach was used to assign participants to four outcome groups: no disorder, tobacco dependence (TD) only, alcohol use disorder (AUD) only, and comorbid (both). Multinomial logistic regression was used to determine the association between partner general and substance-specific environments and single or dual alcohol and tobacco use disorder diagnosis in young adulthood (ages 24-33, n=628). Previous heavy alcohol and tobacco use were controlled for, as were dispositional characteristics, gender, ethnicity, adult SES, and adult depression. Greater partner conflict increased the likelihood of being comorbid compared to having TD only or AUD only. Having a smoking partner increased the likelihood of being comorbid compared to having AUD only, but having a drinking partner did not significantly distinguish being comorbid from having TD only.Findings demonstrated the utility of a comorbidity-based, person-centered approach and the influence of general and tobacco-specific, but not alcohol-specific, partner environments on comorbid alcohol and tobacco use disorders in young adulthood.

The Longitudinal Association Between Homelessness, Injection Drug Use, and Injection-Related Risk Behavior Among Persons With A History Of Injection Drug Use In Baltimore, MD. Linton SL, Celentano DD, Kirk GD, Mehta SH. Drug Alcohol Depend. 2013; 132(3): 457-465.

Few studies have assessed the temporal association between homelessness and injection drug use, and injection-related risk behavior. Among a cohort of 1405 current and former injection drug users in follow-up from 2005 to 2009, the authors used random intercept models to assess the temporal association between homelessness and subsequent injection drug use, and to determine whether the association between homelessness and sustained injection drug use among active injectors differed from the association between homelessness and relapse among those who stopped injecting. The authors also assessed the association between homelessness and subsequent injection-related risk behavior among participants who injected drugs consecutively across two visits. Homelessness was categorized by duration: none, <1 month, and 1 month. Homelessness was reported on at least one occasion by 532 (38%) participants. The relationship between homelessness and subsequent injection drug use was different for active injectors and those who stopped injecting. Among those who stopped injecting, homelessness was associated with relapse [<1 month: AOR=1.67, 95% CI (1.01, 2.74); 1 month: AOR=1.34 95% CI (0.77, 2.33)]. Among active injectors, homelessness was not associated with sustained injection drug use [<1 month: AOR=1.03, 95% CI (0.71, 1.49); 1 month: AOR=0.81 95% CI (0.56, 1.17)]. Among those injecting drugs across two consecutive visits, homelessness 1 month was associated with subsequent injection-related risk behavior [AOR=1.61, 95% CI (1.06, 2.45)]. Homelessness appears to be associated with relapse and injection-related risk behavior. Strengthening policies and interventions that prevent homelessness may reduce injection drug use and injection-related risk behaviors.

Antiretroviral Medication Diversion Among HIV-Positive Substance Abusers In South Florida. Surratt HL, Kurtz SP, Cicero TJ, O'Grady C, Levi-Minzi MA. Am J Public Health. 2013; 103(6): 1026-1028.

The high cost of life-saving antiretroviral (ARV) therapy for HIV represents an expense that impedes accessibility and affordability by patients. This price structure also appears to motivate the diversion of ARVs and the targeting of HIV-positive patients by pill brokers in the illicit market. The authors' field research with indigent, HIV-positive substance abusers links ARV diversion to high levels of competing needs, including psychiatric disorders, HIV stigma, and homelessness. Interventions to reduce diversion must address the needs of highly vulnerable patients.

The Association Between Law Enforcement Encounters and Syringe Sharing Among IDUs On Skid Row: A Mixed Methods Analysis. Surratt HL, Kurtz SP, Cicero TJ, O'Grady C, Levi-Minzi MA. Am J Public Health. 2013; 103(6): 1026-1028.

The legal environment is one factor that influences injection drug users' (IDUs) risk for HIV and other bloodborne pathogens such as hepatitis C virus (HCV). The authors examined the association between law enforcement encounters (i.e., arrests and citations) and receptive syringe sharing among IDUs in the context of an intensified policing effort. They conducted a mixed methods analysis of 30 qualitative and 187 quantitative interviews with IDUs accessing services at a Los Angeles, CA syringe exchange program from 2008 to 2009. Qualitative findings illustrate concerns related to visibility, drug withdrawal, and previous history of arrest/

incarceration. In quantitative analysis, the number of citations received, current homelessness, and perceiving that being arrested would be a "big problem" were independently associated with recent syringe sharing. Findings illustrate some of the unintended public health consequences associated with intensified street-level policing, including risk for HIV and HCV transmission. Wagner KD, Simon-Freeman R, Bluthenthal RN. AIDS Behav. 2013; 17(8): 2637-2643.

Patterns Of Injection Drug Use Cessation During An Expansion Of Syringe Exchange Services In A Canadian Setting. Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood E. Drug Alcohol Depend. 2013; 132(3): 535-540.
Needle and syringe programmes (NSPs) have been shown to reduce HIV risk among people who inject drugs (IDUs). However, concerns remain that NSPs delay injecting cessation. Individuals reporting injection drug use in the past six months in the greater Vancouver area were enrolled in the Vancouver Injection Drug Users Study (VIDUS). Annual estimates of the proportion of IDU reporting injecting cessation were generated. Generalized estimating equation (GEE) analysis was used to assess factors associated with injecting cessation during a period of NSP expansion.Between May 1996 and December 2010, the number of NSP sites in Vancouver increased from 1 to 29 (P<0.001). The estimated proportion of participants (n=2710) reporting cessation increased from 2.4% (95% confidence interval [CI]: 0.0-7.0%) in 1996 to 47.9% (95% CI: 46.8-48.9%) in 2010 (P<0.001). In a multivariate GEE analysis, the authors observed an association between increasing calendar year and increased likelihood of injecting cessation (Adjusted Odds Ratio=1.17, 95% CI: 1.15, 1.19, P<0.001). The proportion of IDU reporting injecting cessation increased during a period of NSP expansion, implying that increased NSP availability did not delay injection cessation. These results should help inform community decisions on whether to implement NSPs.

Adolescents' Access To Their Own Prescription Medications In the Home. Ross-Durow PL, McCabe SE, Boyd CJ. J Adolesc Health. 2013; 53(2): 260-264.
The objective of this descriptive study was to determine adolescents' access to their own medications at home, specifically prescription pain, stimulant, antianxiety, and sedative medications. Semistructured interviews were conducted with a cohort of 501 adolescents from two southeastern Michigan school districts. Participants were asked what medications had been prescribed to them during the previous 6 months; if they had received prescription medications, they were asked in-depth questions about them, including how medications were stored and supervised at home. The sample was comprised of adolescents in the 8th and 9th grades, and 50.9% were male. Participants were primarily white (72.9%, n = 365) or African-American (21.6%, n = 108). Slightly less than half of the adolescents (45.9%, n = 230) reported having been prescribed medications in the previous 6 months. Of this group, 14.3% (n = 33) had been prescribed pain medications, 9.6% (n = 22) stimulants, 1.7% (n = 4) antianxiety medications, and .9% (n = 2) sedatives. In total, 57 adolescents were prescribed medications in the pain, stimulant, antianxiety, or sedative categories (including controlled medications), and the majority (73.7%, n = 42) reported that they had unsupervised access to medications with abuse potential. The majority of adolescents who were prescribed medications in the pain, stimulant, antianxiety, or sedative categories during the previous 6 months had unsupervised access to them at home. It is critical that clinicians educate parents and patients about the importance of proper storage and disposal of medications, particularly those with abuse potential.

Advances In the Science Of Adolescent Drug Involvement: Implications For Assessment and Diagnosis - Experience From The United States. Winters KC. Curr Opin Psychiatry. 2013; 26(4): 318-324.

Adolescence is a developmental period characterized by relatively high rates of substance use and substance use disorders. Precise assessment and classification of adolescent drug use behaviors are essential in gaining an accurate understanding of the nature and extent of adolescent drug use, and possible intervention or treatment needs. There has been a select group of recently published research reports and manuscripts that address critical and emerging issues pertaining to the classification and assessment of alcohol and other drug use behaviors among adolescents. An overview of these publications is provided and their clinical relevance is discussed.The paper will focus on recent research, most from the United States, that addresses four main issues. One is the application of the new DSM-5 criteria to adolescents, including the advantages and disadvantages of the new criteria for substance use disorders. The second issue pertains to advances in instrumentation that provide new tools for researchers and clinicians in assessing substance use in adolescents. A significant public health issue is addressed as the third theme in the paper - screening for alcohol abuse in college settings. Finally, the paper reviews how the emerging science of brain development can inform the assessment process. Recent advances in the adolescent drug abuse assessment field continue to inform clinical service and research. As a whole, these advances have strengthened the field, but continued research is needed to further refine assessment practices and standards and to better understand how to define a substance use disorder in youth.

Examining Links Between Sexual Risk Behaviors and Dating Violence Involvement As A Function Of Sexual Orientation. Hipwell AE, Stepp SD, Keenan K, Allen A, Hoffmann A, Rottingen L, McAloon R. J Pediatr Adolesc Gynecol. 2013; 26(4): 212-218.

The aim of this study was to examine the association between dating violence perpetration and victimization and sexually risky behaviors among sexual minority and heterosexual adolescent girls. Adolescent girls reported on sexual orientation, sexual behaviors, and risk-taking, and their use of, and experience with, dating violence in the past year. Data were analyzed using multinomial regression adjusted for race, poverty, living in a single parent household, and gender of current partner to examine (1) whether sexual minority status was associated with sexual risk behaviors after sociodemographic correlates of sexual risk were controlled; and (2) whether dating violence context accounted for elevated risk. Urban, population-based sample of girls interviewed in the home.1,647 adolescent girls (38% European American, 57% African American, and 5% other) aged 17 years. Over one-third of the sample lived in poverty. Sexual minority status differentiated girls engaging in high sexual risk-taking from those reporting none, after controlling for sociodemographic and relationship characteristics. Dating violence perpetration and victimization made unique additional contributions to this model and did not account for the elevated risk conferred by sexual minority status. Sexual minority girls (SMGs) were more likely than heterosexual girls to report high sexual risk-taking and teen dating violence victimization. As with heterosexual girls, sexual risk-taking among SMGs was compounded by dating violence, which was not explained by partner gender. Adolescent girls' risky sexual behavior may be reduced by interventions for teen dating violence regardless of sexual minority status.

Toward Rigorous Idiographic Research In Prevention Science: Comparison Between Three Analytic Strategies For Testing Preventive Intervention In Very Small Samples. Ridenour TA, Pineo TZ, Maldonado Molina MM, Hassmiller Lich K. Prev Sci. 2013; 14(3): 267-278.

Psychosocial prevention research lacks evidence from intensive within-person lines of research to understand idiographic processes related to development and response to intervention. Such data could be used to fill gaps in the literature and expand the study design options for prevention researchers, including lower-cost yet rigorous studies (e.g., for program evaluations), pilot studies, designs to test programs for low prevalence outcomes, selective/indicated/adaptive intervention research, and understanding of differential response to programs. This study compared three competing analytic strategies designed for this type of research: autoregressive moving average, mixed model trajectory analysis, and P-technique. Illustrative time series data were from a pilot study of an intervention for nursing home residents with diabetes (N=4) designed to improve control of blood glucose. A within-person, intermittent baseline design was used. Intervention effects were detected using each strategy for the aggregated sample and for individual patients. The P-technique model most closely replicated observed glucose levels. ARIMA and P-technique models were most similar in terms of estimated intervention effects and modeled glucose levels. However, ARIMA and P-technique also were more sensitive to missing data, outliers and number of observations. Statistical testing suggested that results generalize both to other persons as well as to idiographic, longitudinal processes. This study demonstrated the potential contributions of idiographic research in prevention science as well as the need for simulation studies to delineate the research circumstances when each analytic approach is optimal for deriving the correct parameter estimates.

"Becoming Bold": Alcohol Use and Sexual Exploration among Black and Latino Young Men Who Have Sex with Men (YMSM). Mutchler MG, McDavitt B, Gordon KK. J Sex Res. 2013.

Alcohol use is correlated with unprotected sex, which may place young men who have sex with men (YMSM) who use alcohol with sex at increased risk for contracting HIV. However, little is known about how this link develops. This study used qualitative interviews to explore how alcohol became associated with sex and sexual risk among YMSM. The authors purposively sampled 20 Black and 20 Latino YMSM (N=40), ages 21 to 24, who used substances (alcohol, marijuana, and crystal methamphetamine) with sex. Interviews focused on participants' personal histories to trace how these associations developed for each individual. Drawing on sexual script, emotion regulation, and alcohol expectancy theories, analyses followed a modified grounded theory approach. Participants stated that alcohol enabled them to engage in sexual behaviors with men that they wanted to try, allowing them to be more "bold," overcome stigma about homosexuality, and feel increased comfort with their sexual desires and identities. The use of alcohol during sex was helpful to some of the participants but could also lead to sexual risk behaviors. Intervention programs seeking to reduce alcohol misuse and sexual risk should take into account how YMSM conceptualize associations between alcohol and sex. These programs may be more effective if they provide support for sexual identity exploration.

The Role Of Depression and Social Support In Non-Fatal Drug Overdose Among A Cohort Of Injection Drug Users In A Canadian Setting. Pabayo R, Alcantara C, Kawachi I, Wood E, Kerr T. Drug Alcohol Depend. 2013; 132(3): 603-609.
Non-fatal overdose remains a significant source of morbidity among people who inject drugs (IDU). Although depression and social support are important in shaping the health of IDU, little is known about the relationship between these factors and overdose. Therefore, the authors sought to determine whether depressive symptoms and social support predicted non-fatal overdose among IDU in a Canadian setting. Data were derived from three prospective cohorts of people who use drugs: the Vancouver Injection Drug Users Study (VIDUS), the ACCESS Cohort, and the At-Risk Youth Study (ARYS). Multilevel modeling was used to determine if depression and social support were significant predictors of non-fatal overdose across time. Analyses were stratified by sex. There were 1931 participants included in this analysis, including 653 (33.8%) females and 69 (3.6%) youth 20 years old or younger. Depressed men (adjusted odds ratio [AOR]=1.53, 95% confidence intervals [CI]=1.25, 1.87) and women (adjusted odds ratio [AOR]=2.23, 95% confidence intervals [CI]=1.65, 3.00) were more likely to experience a non-fatal overdose. Further, among women, those who reported having 3 or more persons they could rely upon for social support were less likely to experience a non-fatal overdose (AOR=0.54, 95% CI 0.31, 0.93). Although depression was a significant predictor of non-fatal drug overdose, social support was a significant predictor among women only. Possible strategies to prevent non-fatal overdose may include identifying IDU experiencing severe depressive symptoms and providing targeted mental health treatments and mobilizing interpersonal social support among IDU, especially among women.

Exploring the Spread Of Methamphetamine Problems Within California, 1980 to 2006. Ponicki WR, Waller LA, Remer LG, Gruenewald PJ. GeoJournal. 2013; 78(3): 451-462.
The introduction and spread of high potency methamphetamine has led to dramatic increases in drug-related problems in California. Prior research suggests that drug abuse rates are related to local demographic and economic characteristics, law enforcement activities, and sentencing practices. Methamphetamine abuse in particular has been shown to be reduced by laws regulating the raw materials needed for its production. This research models the regional effects of such laws on the spatio-temporal patterns of growth of methamphetamine-related problems across California from 1980 to 2006. Amphetamine-related arrests and hospital discharges related to amphetamine abuse/dependence were assembled for California counties over the years 1980 through 2006. Varying-parameter Bayesian space-time models were used to relate the implementation of major laws controlling the distribution of methamphetamine precursors to observed patterns of arrests and discharges and to allow such associations to vary by location. The models used conditionally autoregressive (CAR) Bayesian spatial priors to allow spatial correlation in estimation of county-specific growth in these measures over three distinct time periods: before the 1989 law, between the 1989 and 1997 laws, and after the 1997 law. Growth of arrests and discharges were related to demographic and economic indicators to determine geographic areas more or less susceptible to the spread of methamphetamine problems. Although both problem measures increased during all three periods, each of the precursor laws was associated with short-term reductions in the growth of arrests and discharges. Growth was greatest in central California counties prior to 1989 and increased in coastal counties in later years. From 1980 to 1989 growth was highest for counties with low incomes and high proportions of white residents, while 1989-1997 growth was highest in counties with fewer

whites and more Hispanics. Growth after 1997 was not significantly associated with county characteristics.This research demonstrates that the precursor laws did suppress the growth of methamphetamine related arrests and hospital discharges. It also demonstrates specific geographic patterns in the growth of methamphetamine arrests and abuse across California during this time. Early patterns of growth were related to economic and demographic characteristics, while later patterns were not. This suggests that some counties were uniquely susceptible to the early spread of the methamphetamine epidemic, although problems eventually grew dramatically in all California counties.

Higher Quality Communication and Relationships Are Associated With Improved Patient Engagement In HIV Care. Flickinger TE, Saha S, Moore RD, Beach MC. J Acquir Immune Defic Syndr. 2013; 63(3): 362-366.
Patient retention in HIV care may be influenced by patient-provider interactions. In an urban, academic HIV clinic, 1363 patients rated the quality of communication and relationships with their providers on 5 domains. The authors used linear regressions to investigate associations between these 5 domains and appointment adherence. In multivariate analysis, patients kept more appointments if providers treated them with dignity and respect, listened carefully to them, explained in ways they could understand, and knew them as persons. Being involved in decisions was not significantly associated with appointment adherence. Enhancing providers' skills in effective communication and relationship building may improve patient retention in HIV care.

Are There Differences Between Young African-American and European-American Women In The Relative Influences Of Genetics Versus Environment On Age At First Drink and Problem Alcohol Use? Sartor CE, Nelson EC, Lynskey MT, Madden PAF, Heath AC, Bucholz KK. Alcohol Clin Exp Res. 2013; 37(11): 1939-1946.
Differences in age at initiation of alcohol use and rates of problem drinking between African Americans and European Americans are well documented, but the association between early and problem use-and distinctions by ethnic group in this association-have yet to be examined in a genetically informative framework. Data were derived from a longitudinal study of female twins in Missouri. The sample was composed of 3,532 twins (13.6% African-American [AA], 86.4% European-American [EA]), who participated in the fourth wave of data collection and reported consumption of at least 1 alcoholic drink over the lifetime. Mean age at Wave 4 was 21.7 (range=18 to 29) years. Twin modeling was conducted to estimate the relative contributions of additive genetic (A), shared environmental (C), and unique environmental (E) factors to variation in age at first drink and problem alcohol use and the cross-phenotype overlap in these influences. Early initiation of alcohol use predicted problem use in EA but not AA women. Separate AA and EA twin models produced substantially different estimates (but not statistically different models) of the relative contributions of A and C to problem alcohol use but similar genetic correlations between the phenotypes. Whereas 33% of the variance in the EA model of problem use was attributed to C, no evidence for C was found in the AA model. Heritability estimates for problem alcohol use were 41% in the AA model, 21% in the EA model. Evidence for A and C were found in both AA and EA models of age at first drink, but the A estimate was higher in the EA than AA model (44% vs. 26%). Findings are suggestive of distinctions between AA versus EA women in the relative contribution of genetic and environmental influences on the development of problem drinking.

Individual, Interpersonal, and Social-Structural Correlates Of Involuntary Sex Exchange Among Female Sex Workers In Two Mexico-U.S. Border Cities. Goldenberg SM, Rangel G, Staines H, Vera A, Lozada R, Nguyen L, Silverman JG, Strathdee S. J Acquir Immune Defic Syndr. 2013; 63(5): 639-646.

The aim of this study was to investigate individual, interpersonal, and social-structural factors associated with involuntary sex exchange among female sex workers (FSWs) along the Mexico-U.S. border. In 2010 to 2011, 214 FSWs from Tijuana (n = 106) and Ciudad Juarez (n = 108) aged 18 years who reported lifetime use of heroin, cocaine, crack, or methamphetamine, having a stable partner, and having sold/traded sex in the past month completed quantitative surveys and HIV/sexually transmitted infection testing. Logistic regression was used to identify correlates of involuntary sex exchange among FSWs. Of 214 FSWs, 31 (14.5%) reported involuntary sex exchange. These women were younger at sex industry entry [adjusted odds ratio (AOR): 0.84/1-year increase, 95% confidence interval (CI): 0.72 to 0.97] and were significantly more likely to service clients whom they perceived to be HIV/sexually transmitted infection-infected (AOR: 12.41, 95% CI: 3.15 to 48.91). In addition, they were more likely to have clients who used drugs (AOR: 7.88, 95% CI: 1.52 to 41.00), report poor working conditions (AOR: 3.27, 95% CI: 1.03 to 10.31), and report a history of rape (AOR: 4.46, 95% CI: 1.43 to 13.91). Involuntary sex exchange is disproportionate among FSWs who begin to exchange sex at a younger age, and these women experience elevated risk of violence and HIV/STIs related to their clients' behaviors and their working conditions. These data suggest the critical need for evidence-based approaches to preventing sexual exploitation of women and girls and to reducing harm among current sex workers. Multilevel interventions for all females who exchange sex and their clients that target interpersonal and social-structural risks (eg, measures to improve safety and reduce exploitation within the workplace) are needed.

Personality and Cognitive Decline In The Baltimore Epidemiologic Catchment Area Follow-Up Study. Hock RS, Lee HB, Bienvenu OJ, Nestadt G, Samuels JF, Parisi JM, Costa Jr, PT, Spira AP. Am J Geriatr Psychiatry. 2013.

The objective of this study was to determine the association between personality domains and 11-year cognitive decline in a sample from a population-based study. Data from Waves 3 (1993-1996) and 4 (2003-2004) of the Baltimore cohort of the Epidemiologic Catchment Area (ECA) study were used for analyses. The sample included 561 adults (mean age SD: 45.2 10.78 years) who completed the NEO Personality Inventory-Revised prior to Wave 4. Participants also completed the Mini-Mental State Examination (MMSE) and immediate and delayed word recall tests at Wave 3, and at Wave 4, 10.9 0.6 years later. In models adjusted for baseline cognitive performance, demographic characteristics, medical conditions, depressive symptoms, and psychotropic medication use, each 10-point increase in Neuroticism T-scores was associated with a 0.15-point decrease in MMSE scores (B=-0.15, 95% confidence interval [CI]:-0.30,-0.01), whereas each 10-point increase in Conscientiousness T-scores was associated with a 0.18-point increase on the MMSE (B= 0.18, 95% CI: 0.04, 0.32) and a 0.21-point increase in immediate recall (B= 0.21, 95% CI: 0.003, 0.41) between baseline and follow-up. Findings suggest that greater Neuroticism is associated with decline, and greater Conscientiousness is associated with improvement in performance on measures of general cognitive function and memory in adults. Further studies are needed to determine the extent to which personality traits in midlife are associated with clinically significant cognitive outcomes in older adults, such as mild cognitive

impairment and dementia, and to identify potential mediators of the association between personality and cognitive trajectories.

Trajectories Of Reinforcement Sensitivity During Adolescence and Risk For Substance Use. Colder CR, Hawk Jr, LW, Lengua LJ, Wiezcorek W, Eiden RD, Read JP. J Res Adolesc. 2013; 23(2): 345-356.
Developmental neuroscience models suggest that changes in responsiveness to incentives contribute to increases in adolescent risk behavior, including substance use. Trajectories of sensitivity to reward (SR) and sensitivity to punishment (SP) were examined and tested as predictors of escalation of early substance use in a community sample of adolescents (N=765, mean baseline age 11.8 years, 54% female). SR and SP were assessed using a laboratory task. Across three annual assessments, SR increased, and rapid escalation was associated with increases in substance use. SP declined and was unrelated to substance use. Findings support contemporary views of adolescent brain development, and suggest that early adolescent substance use is motivated by approach responses to reward, rather than failure to avoid potential aversive consequences.

Drug and Alcohol Trajectories Among Adults With Schizophrenia: Data From The CATIE Study. Van Dorn RA, Desmarais SL, Tueller SJ, Jolley JM, Johnson KL, Swartz MS. Schizophr Res. 2013; 148(1-3): 126-129.
The primary aim is to describe drug and alcohol trajectories in adults with schizophrenia. Growth mixture models were used to examine disordered and non-disordered use and abstinence in the Clinical Antipsychotic Trials of Intervention Effectiveness study. Five classes - always abstinent; fluctuating use, abuse, and occasional abstinence; occasional (ab)use; stopped (ab)use; abusing - fit best. Overlap exists between always abstinent drug and alcohol classes; less overlap exists across other classes. There is heterogeneity in drug and alcohol use among adults with schizophrenia. The lack of overlap between classes, save always abstinent, suggests modeling drug and alcohol use separately.

The Effects Of Exposure To Violence and Victimization Across Life Domains On Adolescent Substance Use. Wright EM, Fagan AA, Pinchevsky GM. Child Abuse Negl. 2013.
This study uses longitudinal data from the Project on Human Development in Chicago Neighborhoods (PHDCN) to examine the effects of exposure to school violence, community violence, child abuse, and parental intimate partner violence (IPV) on youths' subsequent alcohol and marijuana use. The authors also examine the cumulative effects of being exposed to violence across these domains. Longitudinal data were obtained from 1,655 adolescents and their primary caregivers participating in the PHDCN. The effects of adolescents' exposure to various forms of violence across different life domains were examined relative to adolescents' frequency of alcohol and marijuana use three years later. Multivariate statistical models were employed to control for a range of child, parent, and family risk factors. Exposure to violence in a one-year period increased the frequency of substance use three years later, though the specific relationships between victimization and use varied for alcohol and marijuana use. Community violence and child abuse, but not school violence or exposure to IPV, were predictive of future marijuana use. None of the independent measures of exposure to violence significantly predicted future alcohol use. Finally, the accumulation of exposure to violence across life domains was detrimental to both future alcohol and marijuana use. The findings support prior research

indicating that exposure to multiple forms of violence, across multiple domains of life, negatively impacts adolescent outcomes, including substance use. The findings also suggest that the context in which exposure to violence occurs should be considered in future research, since the more domains in which youth are exposed to violence, the fewer "safe havens" they have available. Finally, a better understanding of the types of violence youth encounter and the contexts in which these experiences occur can help inform intervention efforts aimed at reducing victimization and its negative consequences.

Toward Primary Prevention Of Extra-Medical Oxycontin Use Among Young People. Deandrea DC, Troost JP, Anthony JC. Prev Med. 2013; 57(3): 244-246.
The prevention research context includes current epidemic levels of hazards associated with extra-medical use of OxyContin (to get high or otherwise outside prescribed boundaries) among teenagers and young adults, and a recent OxyContin re-formulation with an intent to reduce these hazards, plus hope for possibly beneficial primary prevention impact. The aim is to create a benchmark of risk estimates for the years just prior to OxyContin re-formulation in anticipation of potential public health benefit in future years, with a focus on teens and the youngest adults in the United States, and to compare two methods for estimating peak risk. The data are from nationally representative probability sample surveys of 12-21 year olds, yielding estimates for incidence of extra-medical OxyContin use. Samples are of the non-institutionalized United States population, recruited and assessed in National Surveys on Drug Use and Health (NSDUH), each year from 2004 through 2008. In aggregate, the sample includes 135,552 young people who had not used OxyContin extra-medically prior to their year of survey assessment. The main outcome was the estimated population-level age-specific incidence of extra-medical OxyContin use, 2004-2008. The authors found that during the 2004-2008 interval the estimated risk accelerated from age 12 years, reached a peak value in mid-adolescence at roughly five newly incident users per 1000 persons per year (95% confidence intervals, 0.3%, 0.7%), and then declined. A meta-analysis approach to year-by-year data differentiated age patterns more clearly than a pooled estimation approach. Studying young people in the United States, the authors have discovered that the risk of starting to use OxyContin extra-medically rises to a peak by mid-adolescence and then declines. From a methods standpoint, the meta-analysis serves well in this context; there is no advantage to pooling survey data across years. The authors also discovered that during any given year a pediatrician might rarely see even one patient who has just started to use OxyContin to get high or for other extra-medical purposes. Implications for screening are discussed.

Childhood Sexual Experiences Among Substance-Using Non-Gay Identified Black Men Who Have Sex With Men and Women. Benoit E, Downing Jr, MJ. Child Abuse Negl. 2013; 37(9): 679-690.
This study explored potential variations in childhood sexual abuse (CSA) by examining qualitative accounts of first sexual experiences among non-disclosing, non-gay identified Black men who have sex with men and women (MSMW). The authors analyzed data from semi-structured qualitative interviews with 33 MSMW who described first sexual experiences with male and female partners. Thematic analysis revealed four patterns of first sexual experiences including: unwanted sexual experiences with a male or female consistent with definitions of childhood sexual abuse; consensual sex with an older male or female; bodily exploration with another male or female child; and consensual sex with a peer-age female. Most of the experiences described by participants as consensual with an older male or female, however, met

criteria for childhood sexual abuse found in the extant literature. Several men discussed childhood sexual experiences (CSE) relative to their experiences with alcohol, drugs, and same-sex behavior as adults. Findings suggest that the relationship between CSE and risk-taking behavior may be shaped by whether men perceive their experiences as abusive or consensual, and have implications for researchers, treatment providers and counselors.

Gender and Social Rejection As Risk Factors For Engaging In Risky Sexual Behavior Among Crack/Cocaine Users. Kopetz C, Pickover A, Magidson JF, Richards JM, Iwamoto D, Lejuez CW. Prev Sci. 2013.
Crack/cocaine and engagement in risky sexual behavior represent important contributors to the escalation of the HIV infection among women. Several lines of research have emphasized the role of social factors in women's vulnerability for such practices and stressed the importance of understanding such factors to better inform prevention efforts and improve their effectiveness and efficiency. However, few studies have attempted to pinpoint specific social/contextual factors particularly relevant to high-risk populations such as female crack/cocaine users. Extensive previous research has related the experience of social rejection to a variety of negative outcomes including, but not limited to, various forms of psychopathology, self-defeating, and self-harm behavior. Motivated by this research, the current study explored the role of laboratory-induced social rejection in moderating the relationship between gender and risky sexual behavior among a sample of crack/cocaine users (n=211) at high risk for HIV. The results showed that among women, but not among men, experiencing social rejection was significantly associated with a greater number of sexual partners. Further, experiencing social rejection was not related to the frequency of condom use. Implications for future research, prevention, and treatment are discussed.

Stability and Change Of Genetic and Environmental Effects On the Common Liability To Alcohol, Tobacco, and Cannabis DSM-IV Dependence Symptoms. Palmer RHC, Young SE, Corley RP, Hopfer CJ, Stallings MC, Hewitt JK. Behav Genet. 2013; 43(5): 374-385.
This study investigated the stability of genetic and environmental effects on the common liability to alcohol, tobacco, and cannabis dependence across adolescence and young adulthood. DSM-IV symptom counts from 2,361 adolescents were obtained using a structured diagnostic interview. Several sex-limited longitudinal common pathway models were used to examine gender differences in the magnitude of additive genetic (A), shared environment, and non-shared environmental effects over time. Model fitting indicated limited gender differences. Among older adolescents (i.e., age > 14), the heritability of the latent trait was estimated at 0.43 (0.05, 0.94) during the first wave and 0.63 (0.21, 0.83) during the second wave of assessment. A common genetic factor could account for genetic influences at both assessments, as well as the majority of the stability of SAV over time [rA = 1.00 (0.55, 1.00)]. These results suggest that early genetic factors continue to play a key role at later developmental stages.

A Latent Class Analysis Of External Barriers To Drug Treatment In China. Qi C, Kelly BC, Liu T, Liao Y, Hao W, Wang JA. J Subst Abuse Treat. 2013; 45(4): 350-355.
Drug treatment services of varying types have been scaled up in China over the past decade. Yet, barriers to treatment remain among the population of drug users in China. In this paper, the authors use a person-centered approach to examine external barriers to drug treatment among a sample of Chinese drug users. Specifically, they used a latent class analysis to determine a

typology of external barriers to treatment among a sample of 262 drug users. The results of the analyses suggest three-classes of drug users with respect to their perceptions of external barriers to treatment--Major Barriers, Low Barriers, and Systems-level Barriers--indicating that drug users are a heterogeneous population on this matter. Age and types of drugs used were predictors of class membership. In this regard, different tactics must be utilized in order to successfully reach this wide ranging group of individuals.

Developmental Trajectories Of Acculturation In Hispanic Adolescents: Associations With Family Functioning and Adolescent Risk Behavior. Schwartz SJ, Des Rosiers S, Huang S, Zamboanga BL, Unger JB, Knight GP, Pantin H, Szapocznik J. Child Dev. 2013; 84(4): 1355-1372.
This study examined longitudinal acculturation patterns, and their associations with family functioning and adolescent risk behaviors, in Hispanic immigrant families. A sample of 266 Hispanic adolescents (Mage =13.4) and their primary parents completed measures of acculturation, family functioning, and adolescent conduct problems, substance use, and sexual behavior at five timepoints. Mixture models yielded three trajectory classes apiece for adolescent and parent acculturation. Assimilated adolescents reported the poorest family functioning, but adolescent assimilation negatively predicted adolescent cigarette smoking, sexual activity, and unprotected sex indirectly through family functioning. Follow-up analyses indicated that discrepancies between adolescent and parent family functioning reports predicted these adolescent outcomes. Results are discussed regarding acculturation trajectories, adolescent risk behavior, and the mediating role of family functioning.

Trajectories Of Depressive Symptoms and Suicidality Among Heterosexual and Sexual Minority Youth. Marshal MP, Dermody SS, Cheong J, Burton CM, Friedman MS, Aranda F, Hughes TL. J Youth Adolesc. 2013; 42(8): 1243-1256.
Sexual minority youth report higher rates of depression and suicidality than do heterosexual youth. Little is known, however, about whether these disparities continue as youth transition into young adulthood. The primary goals of this study were to describe and compare trajectories of adolescent depressive symptoms and suicidality among sexual minority and heterosexual youth, examine differences in depressive symptoms and suicidality trajectories across sexual orientation subgroups, and determine whether there are gender differences in these longitudinal disparities. Four waves of data from the National Longitudinal Study of Adolescent Health were analyzed using latent curve modeling (N = 12,379; 53% female). Results showed that the rates of depressive symptoms and suicidality in early adolescence were higher among sexual minority youth than among heterosexual youth, and that these disparities persisted over time as participants transitioned into young adulthood. Consistent with previous cross-sectional studies, the observed longitudinal disparities were largest for females and for bisexually-identified youth. Sexual minority youth may benefit from childhood and early adolescent prevention and intervention programs.

Sustained Hyperresponsiveness Of Dendritic Cells Is Associated With Spontaneous Resolution Of Acute Hepatitis C. Pelletier S, Bedard N, Said E, Ancuta P, Bruneau J, Shoukry NH.. J Virol. 2013; 87(12): 6769-6781.
Some studies have reported that dendritic cells (DCs) may be dysfunctional in a subset of patients with chronic hepatitis C virus (HCV) infection. However, the function of DCs during

acute HCV infection and their role in determining infectious outcome remain elusive. Here, the authors examined the phenotype and function of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) during acute HCV infection. Three groups of injection drug users (IDUs) at high risk of HCV infection were studied: an uninfected group, a group with acute HCV infection with spontaneous resolution, and a group with acute infection with chronic evolution. They examined the frequency, maturation status, and cytokine production capacity of DCs in response to the Toll-like receptor 4 (TLR4) and TLR7/8 ligands lipopolysaccharide (LPS) and single-stranded RNA (ssRNA), respectively. Several observations could distinguish HCV-negative IDUs and acute HCV resolvers from patients with acute infection with chronic evolution. First, the authors observed a decrease in the frequency of mature CD86(+), programmed death-1 receptor ligand-positive (PDL1(+)), and PDL2(+) pDCs. This phenotype was associated with the increased sensitivity of pDCs from resolvers and HCV-negative IDUs versus the group with acute infection with chronic evolution to ssRNA stimulation in vitro. Second, LPS-stimulated mDCs from resolvers and HCV-negative IDUs produced higher levels of cytokines than mDCs from the group with acute infection with chronic evolution. Third, mDCs from all patients with acute HCV infection, irrespective of their outcomes, produced higher levels of cytokines during the early acute phase in response to ssRNA than mDCs from healthy controls. However, this hyperresponsiveness was sustained only in spontaneous resolvers. Altogether, these results suggest that the immature pDC phenotype and sustained pDC and mDC hyperresponsiveness are associated with spontaneous resolution of acute HCV infection.

Correlates Of Unprotected Sexual Intercourse Among Women Who Inject Drugs Or Who Have Sexual Partners Who Inject Drugs In St. Petersburg, Russia. Abdala N, Hansen NB, Toussova OV, Krasnoselskikh TV, Verevochkin S, Kozlov AP, Heimer R. J Fam Plann Reprod Health Care. 2013; 39(3): 179-185.

To assess risk for unintended pregnancy, this study describes the correlates of unprotected sexual intercourse (UPSI) among women who inject illicit drugs or who have sexual partners who inject drugs in St. Petersburg, Russia. Data from a cross-sectional survey and biological test results collected between 2005 and 2008 from 202 Russian women (143 drug injectors and 59 non-drug injectors) were analysed. Multivariate regression was used to investigate the correlates of UPSI occurring at the women's last sexual act. Independent variables included socio-demographics, age at sexual debut, first sexual encounter perceived as involuntary, number of pregnancies and number of children for which the participant is the primary caretaker, heavy sporadic drinking (i.e. consuming more than five drinks in 24 hours at least twice a month), at-risk drinking per the Alcohol Use Disorder Identification Test (AUDIT-C) score, and sexually transmitted infections (HIV-1, syphilis serology, Chlamydia trachomatis and Neisseria gonorrheae). Sixty-seven percent of women reported UPSI at last intercourse. UPSI was independently associated with heavy sporadic drinking [odds ratio (OR) 2.8, 95% CI 1.2-6.6] and having been pregnant (OR 2.25, 95% CI 1.1-4.6). Despite the high risk for HIV acquisition or transmission and unintended pregnancy, condom use among the study population is low. Programmes to investigate and improve contraceptive use, including condom use, among this vulnerable group of women are needed. Such programmes may require identifying and targeting female reproductive health concerns and problem drinking, particularly heavy sporadic drinking, rather than conventional measures of alcohol misuse.

Correlates Of Self-Efficacy For Condom Use Among Male Clients Of Female Sex Workers In Tijuana, Mexico. Volkmann T, Wagner KD, Strathdee SA, Semple SJ, Ompad DC, Chavarin CV, Patterson TL. Arch Sex Behav. 2013.
Male clients of female sex workers (FSWs) in Tijuana, Mexico engage in high levels of unprotected sex. While behavioral change theories posit that self-efficacy predicts condom use, correlates of self-efficacy for condom use remain largely unstudied. The authors examined these correlates among male clients of FSWs in Tijuana. Eligible male clients were at least 18 years of age, HIV-negative, lived in Tijuana or San Diego, reported unprotected sex with a Tijuana FSW at least once in the past 4months, and agreed to be treated for sexually transmitted infections (STIs). Participants completed an interviewer-administered questionnaire including demographics, substance use, psychosocial and psychosexual characteristics (e.g., outcome expectancies for negotiation of safer sex, social support, and sexual sensation seeking), and sexual behaviors. Participants also underwent HIV/STI testing. A stepwise hierarchical multiple regression analysis identified correlates of self-efficacy for condom use. Of 393 male clients, median age was 37 years. Participants were mostly Spanish-speaking and employed. Factors independently associated with higher self-efficacy for condom use were higher positive outcome expectancies for negotiation of safer sex, lower sexual sensation seeking scores, and higher social support scores. Both psychosocial and psychosexual factors may influence self-efficacy for condom use among male clients of FSWs. These factors represent central constructs in sociocognitive models that explain behavioral change and could be intervention targets for improving self-efficacy for condom use and, ultimately, safer sex behavior.

HIV Information and Behavioral Skills Moderate the Effects Of Relationship Type and Substance Use On HIV Risk Behaviors Among African American Youth. Mustanski B, Byck GR, Newcomb ME, Henry D, Bolland J, Dick D. AIDS Patient Care STDS. 2013; 27(6): 342-351.
The HIV/AIDS epidemic is disproportionately impacting young African Americans. Efforts to understand and address risk factors for unprotected sex in this population are critical in improving prevention efforts. Situational risk factors, such as relationship type and substance use before sex, are in need of further study. This study explored how established cognitive predictors of risky sexual behavior moderated the association between situational factors and unprotected sex among low-income, African American adolescents. The largest main effect on the number of unprotected sex acts was classifying the relationship as serious (event rate ratio=10.18); other significant main effects were alcohol use before sex, participant age, behavioral skills, and level of motivation. HIV information moderated the effect of partner age difference, motivation moderated the effects of partner age difference and drug use before sex, and behavioral skills moderated the effects of alcohol and drug use before sex. This novel, partnership-level approach provides insight into the complex interactions of situational and cognitive factors in sexual risk taking.

Domains of Acculturation and Their Effects on Substance Use and Sexual Behavior in Recent Hispanic Immigrant Adolescents. Schwartz SJ, Unger JB, Des Rosiers SE, Lorenzo-Blanco EI, Zamboanga BL, Huang Shi, Baezconde-Garbanati L, Villamar JA, Soto DW, Pattarroyo M, Szapocznik J. Prev Sci. 2013.
This study evaluated the immigrant paradox by ascertaining the effects of multiple components of acculturation on substance use and sexual behavior among recently immigrated Hispanic

adolescents primarily from Mexico (35%) and Cuba (31%). A sample of 302 adolescents (53% boys; mean age 14.51 years) from Miami (n=152) and Los Angeles (n=150) provided data on Hispanic and US cultural practices, values, and identifications at baseline and provided reports of cigarette use, alcohol use, sexual activity, and unprotected sex approximately 1year later. Results indicated strong gender differences, with the majority of significant findings emerging for boys. Supporting the immigrant paradox (i.e., that becoming oriented toward US culture is predictive of increased health risks), individualist values predicted greater numbers of oral sex partners and unprotected sex occasions for boys. However, contrary to the immigrant paradox, for boys, both US practices and US identification predicted less heavy drinking, fewer oral and vaginal/anal sex partners, and less unprotected vaginal/anal sex. Ethnic identity (identification with one's heritage culture) predicted greater numbers of sexual partners but negatively predicted unprotected sex. Results indicate a need for multidimensional, multi-domain models of acculturation and suggest that more work is needed to determine the most effective ways to culturally inform prevention programs.

Intimate Partner Violence Victimization and Cigarette Smoking: A Meta-Analytic Review.
Crane CA, Hawes SW, Weinberger AH. Trauma Violence Abuse. 2013; 14(4): 305-315.
The current meta-analytic review represents the first comprehensive empirical evaluation of the strength of the relationship between intimate partner violence (IPV) victimization and cigarette smoking. Thirty-nine effect sizes, drawn from 31 peer-reviewed publications, determined the existence of a small to medium composite effect size for the victimization-smoking relationship (d = .41, 95% confidence interval = [.35, .47]). Results indicate that victims of IPV are at greater smoking risk than nonvictims. Subsequent moderator analyses indicated that the association between victimization and smoking is moderately stronger among pregnant compared to nonpregnant victims. The strength of the victimization-smoking relationship did not differ by relationship type or ethnicity. More research is needed on the smoking behavior of male victims, victims of psychological violence, and victims who identify as Latino/Latina. It would be useful for professionals working with IPV victims to assess for smoking and incorporate smoking prevention and cessation skills in intervention settings.

Child Physical and Sexual Abuse and Cigarette Smoking In Adolescence and Adulthood.
Kristman-Valente AN, Brown EC, Herrenkohl TI. J Adolesc Health. 2013; 53(4): 533-538.
Analyses used data from an extended longitudinal study to examine the relationship between childhood physical and sexual abuse (CPA and CSA, respectively) and adolescent and adult smoking behavior. Two questions guided the study: (1) Is there an association between childhood abuse and adolescent and adult smoking behavior? (2) Does the relationship between childhood abuse and later cigarette smoking differ for males and females? A censored-inflated path model was used to assess the impact of child abuse on adolescent and adult lifetime smoking prevalence and smoking frequency. Gender differences in significant model paths were assessed using a multiple-group approach. Results show no significant relation between CPA or CSA and risk of having ever smoked cigarettes in adolescence or adulthood. However, for males, both CPA and CSA had direct effects on adolescent smoking frequency. For females, only CSA predicted increased smoking frequency in adolescence. Adolescent smoking frequency predicted adult smoking frequency more strongly for females compared with males.CPA and CSA are risk factors for higher frequency of smoking in adolescence. Higher frequency of cigarette smoking in adolescence increases the risk of higher smoking frequency in adulthood. Results underscore

the need for both primary and secondary prevention and intervention efforts to reduce the likelihood of childhood abuse and to lessen risk for cigarette smoking among those who have been abused.

Putting The 'Epi' Into Epigenetics Research In Psychiatry. El-Sayed AM, Koenen KC, Galea S. J Epidemiol Community Health. 2013; 67(7): 610-616.
During the past two decades, research concerned with the aetiology of psychopathology has generally progressed along two separate paths: investigations that have characterized the roles played by environmental determinants such as childhood adversity in the development of psychopathology, and those that have focused on neurobiological processes involving genetic and intracellular pathways. Epigenetic modifications, functionally relevant changes to gene expression that do not reflect changes in gene sequence, may explain how environmental exposures 'get under the skin' to modify the expression of genes and produce phenotypic variability. The potential of epigenetic research to unify two disparate strands of inquiry has contributed to substantial, and growing, interest in epigenetics in mental health research. However, there are several challenges with which investigators must contend in studies considering the role of epigenetic modifications in psychopathology. These include the development of causal models in study design, considerations about sample size and generalisability, and robust measurement of epigenetic modification. The authors employ an epidemiological lens to discuss these challenges and to provide recommendations for future studies in this area.

Spatial-Temporal Disease Mapping Of Illicit Drug Abuse Or Dependence In the Presence Of Misaligned ZIP Codes. Zhu L, Waller LA, Ma J. GeoJournal. 2013; 78(3): 463-474.
Geo-referenced data often are collected in small, administrative units such as census enumeration districts or postal code areas. Such areas vary in geographic area and population size and may change over time. In research into drug-related health issues within the United States, U.S. Postal Service ZIP codes represent a commonly used unit for data collection, storage, and spatial analysis because of their widespread availability in health databases through patient contact and billing information. However, the ZIP code was developed for the specific purpose of delivering mail and may be changed at any time, and its design and development does not take into consideration problems that may arise in data collection, analysis, and presentation in health studies. In this paper, the authors propose a spatial hierarchical modeling approach to quantify trends within ZIP-code based counts when some fraction of ZIP codes change over the study period, that is, when the data are spatially misaligned across time. They propose a data vector approach and adjust the spatial auto-correlation structure within their Bayesian hierarchical model to provide inference for their misaligned data. They motivate and illustrate their approach to explore spatio-temporal patterns of amphetamine abuse and/or dependence in Tracy, California over the years 1995-2005. Uncertainty associated with misaligned data is modeled, quantified, and visualized. The approach offers a framework for further investigation into other risk factors in order to more fully understand the dynamics of illicit drug abuse or dependence across time and space in imperfectly measured data.

Normative Perceptions and Past-Year Consequences As Predictors Of Subjective Evaluations and Weekly Drinking Behavior. Merrill JE, Read JP, Colder CR. Addict Behav. 2013; 38(11): 2625-2634.

Problem drinking during the college years continues to be an important area of study. Subjective evaluations of consequences have recently been demonstrated to predict future drinking behavior; however, what predicts those evaluations is yet unknown. Social Learning Theory (SLT) provides a guiding framework in this study. Primary aims are to investigate whether individual differences in past experience with alcohol consequences and normative perceptions of alcohol consequences predict subjective evaluations (i.e., the extent to which consequences are perceived as negative, aversive, or severe) and weekly drinking behavior. The authors also test whether evaluations mediate the influence of past consequences and norms on weekly drinking behavior. Following a baseline assessment, participants (N = 96 regularly drinking college students, 52% female) completed ten weekly web-based surveys on previous week alcohol use, consequences, and subjective evaluations of those consequences. A series of hierarchical linear models were used to test hypotheses. Most mediational pathways were not supported - weekly level evaluations do not appear to fully explain the effect of norms or past experience on weekly level drinking behavior. However, results demonstrated that normative perceptions of and past experience with consequences were associated with both weekly drinking behavior and subjective evaluations, and evaluations remained significant predictors of alcohol use behavior after accounting for these important between-person influences. Findings support the importance placed by SLT on cognition in drinking behavior, and suggest that norms for consequences and subjective evaluations may be appropriate targets of intervention in college students.

Under Treatment Of Pain: A Prescription For Opioid Misuse Among the Elderly? Levi-Minzi MA, Surratt HL, Kurtz SP, Buttram ME. Pain Med. 2013.

The objective of this study was to examine the demographic, physical, and mental health characteristics; current drug use patterns; motivations for use; and diversion sources among elderly prescription opioid misusers. This was a mixed methods design carried out in research field offices, or senior or community center offices in South Florida. Individuals aged 60 and over reporting past 90-day prescription medication misuse served as participants; only prescription opioid misusers (N=88) were included in the final analysis. The Global Appraisal of Individual Needs was the main survey instrument. A subsample of elderly reporting substantial prescription drug misuse were chosen for the in-depth interview (N=30). The mean age was 63.3. Fifty percent reported ever being admitted to a drug treatment program; several endorsed recent illicit drug use: powder cocaine and/or crack (35.2%), marijuana (30.7%), heroin (14.8%). The majority reported past year severe physical pain and discomfort (86.4%), and misuse of their primary opioid for pain (80.7%); over half (52.3%) obtained their primary opioid from their regular doctor. Qualitative data highlight the misuse of prescription opioids due to untreated or undertreated pain. Participants with primary opioid misuse for pain had over 12 times higher odds of obtaining the medication from their regular doctor (odds ratio [OR]=12.22, P=0.002) and had lower odds of using a dealer (OR=0.20, P=0.005). Findings suggest that this group of elderly participants often misuse their own prescriptions for pain management. This study highlights the need to educate prescribing professionals on appropriate pain management for older adults while still being sensitive to issues of substance abuse and dependence.

Associations Between DSM-IV Mental Disorders and Onset Of Self-Reported Peptic Ulcer In The World Mental Health Surveys. Scott KM, Alonso J, de Jonge P, Viana MC, Liu Z, O'Neill S, Aguilar-Gaxiola S, Bruffaerts R, Caldas-de-Almeida JM, Stein DJ, Angermeyer M, Benjet C, de Girolamo G, Firuleasa I-L, Hu C, Kiejna A, Kovess-Masfety V, Levinson D, Nakane Y, Piazza M, Posada-Villa JA, Khalaf MS, Lim CCW, Kessler RC. J Psychosom Res. 2013; 75(2): 121-127.

Recent research demonstrating concurrent associations between mental disorders and peptic ulcers has renewed interest in links between psychological factors and ulcers. However, little is known about associations between temporally prior mental disorders and subsequent ulcer onset. Nor has the potentially confounding role of childhood adversities been explored. The objective of this study was to examine associations between a wide range of temporally prior DSM-IV mental disorders and subsequent onset of ulcer, without and with adjustment for mental disorder comorbidity and childhood adversities. Face-to-face household surveys conducted in 19 countries (n=52,095; person years=2,096,486). The Composite International Diagnostic Interview retrospectively assessed lifetime prevalence and age at onset of 16 DSM-IV mental disorders. Peptic ulcer onset was assessed in the same interview by self-report of physician's diagnosis and year of diagnosis. Survival analyses estimated associations between first onset of mental disorders and subsequent ulcer onset. After comorbidity and sociodemographic adjustment, depression, social phobia, specific phobia, post-traumatic stress disorder, intermittent explosive disorder, alcohol and drug abuse disorders were significantly associated with ulcer onset (ORs 1.3-1.6). Increasing number of lifetime mental disorders was associated with ulcer onset in a dose-response fashion. These associations were only slightly attenuated by adjustment for childhood adversities. A wide range of mental disorders were linked with the self-report of subsequent peptic ulcer onset. These associations require confirmation in prospective designs, but are suggestive of a role for mental disorders in contributing to ulcer vulnerability, possibly through abnormalities in the physiological stress response associated with mental disorders.

The Aftermath Of Public Housing Relocation: Relationship To Substance Misuse. Cooper HL, Bonney LE, Ross Z, Karnes C, Hunter-Jones J, Kelley ME, Rothenberg R. Drug Alcohol Depend. 2013; 133(1): 37-44.

Several cross-sectional studies have examined relationships between neighborhood characteristics and substance misuse. Using data from a sample of African-American adults relocating from U.S. public housing complexes, the authors examined relationships between changes in exposure to local socioeconomic conditions and substance misuse over time. They tested the hypothesis that adults who experienced greater post-relocation improvements in local economic conditions and social disorder would have a lower probability of recent substance misuse. Data were drawn from administrative sources to describe the census tracts where participants lived before and after relocating. Data on individual-level characteristics, including binge drinking, illicit drug use, and substance dependence, were gathered via survey before and after the relocations. Multilevel models were used to test hypotheses.Participants (N=172) experienced improvements in tract-level economic conditions and, to a lesser degree, in social disorder after moving. A one standard-deviation improvement in tract-level economic conditions was associated with a decrease in recent binge drinking from 34% to 20% (p=0.04) and with a decline in using illicit drugs weekly or more from 37% to 16% (p=0.02). A reduction in tract-level alcohol outlet density of >3.0 outlets per square mile predicted a reduction in binge drinking from 32% to 18% at p=0.05 significance level. The authors observed relationships

between improvements in tract-level conditions and declines in substance misuse, providing further support for the importance of the local environment in shaping substance misuse. These findings have important implications for public housing policies and future research.

Risk Factors For Progression To Regular Injection Drug Use Among Street-Involved Youth In A Canadian Setting. Debeck K, Kerr T, Marshall BDL, Simo A, Montaner J, Wood E. Drug Alcohol Depend. 2013.
Street-involved youth are at high risk for experimenting with injection drug use; however, little attention has been given to identifying the factors that predict progression to on-going injecting. Logistic regression was used to identify factors associated with progression to injecting weekly on a regular basis among a Canadian cohort of street-involved youth. Among the authors' sample of 405 youth who had initiated injecting at baseline or during study observation, the median age was 22 years (interquartile range [IQR]=21-24), and 72% (293) reported becoming a regular injector at some point after their first injection experience. Of these, the majority (n=186, 63%) reported doing so within a month of initiating injection drug use. In multivariate analysis, the drug used at the first injection initiation event (opiates vs. cocaine vs. methamphetamine vs. other; all $p>0.05$) was not associated with progression; however, younger age at first injection (adjusted odds ratio [AOR]=1.13), a history of childhood physical abuse (AOR=1.81), prior regular use of the drug first injected (AOR=1.77), and having a sexual partner present at the first injection event (AOR=2.65) independently predicted progression to regular injecting. These data highlight how quickly youth progress to become regular injectors after experimentation. Findings indicate that addressing childhood trauma and interventions such as evidence-based youth focused addiction treatment that could prevent or delay regular non-injection drug use, may reduce progression to regular injection drug use among this population.

The Spatial and Temporal Association Of Neighborhood Drug Markets and Rates Of Sexually Transmitted Infections In An Urban Setting. Jennings JM, Woods SE, Curriero FC. Health Place. 2013; 23: 128-137.
This study examined temporal and spatial relationships between neighborhood drug markets and gonorrhea among census block groups from 2002 to 2005. This was a spatial, longitudinal ecologic study. Poisson regression was used with adjustment in final models for socioeconomic status, residential stability and vacant housing. Increased drug market arrests were significantly associated with a 11% increase in gonorrhea (adjusted relative risk (ARR) 1.11; 95% CI 1.05, 1.16). Increased drug market arrests in adjacent neighborhoods were significantly associated with a 27% increase in gonorrhea (ARR 1.27; 95% CI 1.16, 1.36), independent of focal neighborhood drug markets. Increased drug market arrests in the previous year in focal neighborhoods were not associated with gonorrhea (ARR 1.04; 95% CI 0.98, 1.10), adjusting for focal and adjacent drug markets. While the temporal association was not supported, these findings support an associative link between drug markets and gonorrhea. The findings suggest that drug markets and their associated sexual networks may extend beyond local neighborhood boundaries indicating the importance of including spatial lags in regression models investigating these associations.

Gender Differences In Lifetime Alcohol Dependence: Results From The National Epidemiologic Survey On Alcohol and Related Conditions. Khan S, Okuda M, Hasin DS, Secades-Villa R, Keyes K, Lin K-H, Grant B, Blanco C. Alcohol Clin Exp Res. 2013; 37(10): 1696-1705.

An extensive clinical literature has noted gender differences in the etiology and clinical characteristics of individuals with alcohol dependence (AD). Despite this knowledge, many important questions remain. Using the 2001 to 2002 National Epidemiologic Survey on Alcohol and Related Conditions (n=43,093), the authors examined differences in sociodemographic characteristics, psychiatric and medical comorbidities, clinical correlates, risk factors, and treatment-utilization patterns of men (N=2,974) and women (N=1,807) with lifetime AD. Men with lifetime AD were more likely than women to be diagnosed with any substance use disorder and antisocial personality disorder, whereas women were more likely to have mood and anxiety disorders. After adjusting for sociodemographic characteristics and gender differences in psychiatric comorbidity in the general population, AD was associated with externalizing disorders and any mood disorder among women only. Men with AD met more criteria, had longer episodes, and were younger at the age of first drink. There were no gender differences in remission rates. Women with AD were more likely to have a family and a spouse with history of alcohol use disorders. Treatment rates were low for both genders, and women were more likely to report social stigmatization as a treatment barrier. There are important gender differences in the psychiatric comorbidities, risk factors, clinical characteristics, and treatment-utilization patterns among individuals with lifetime AD.

Illicit and Nonmedical Drug Use Among Asian Americans, Native Hawaiians/Pacific Islanders, and Mixed-Race Individuals. Wu L-T, Blazer DG, Swartz MS, Burchett B, Brady KT, NIDA AAPI Workgroup. Drug Alcohol Depend. 2013.

The racial/ethnic composition of the United States is shifting rapidly, with non-Hispanic Asian-Americans, Native Hawaiians/Pacific Islanders (NHs/PIs), and mixed-race individuals the fastest growing segments of the population. The authors determined new drug use estimates for these rising groups. Prevalences among Whites were included as a comparison. Data were from the 2005-2011 National Surveys on Drug Use and Health. Substance use among respondents aged 12 years was assessed by computer-assisted self-interviewing methods. Respondents' self-reported race/ethnicity, age, gender, household income, government assistance, county type, residential stability, major depressive episode, history of being arrested, tobacco use, and alcohol use were examined as correlates. The authors stratified the analysis by race/ethnicity and used logistic regression to estimate odds of drug use. Prevalence of past-year marijuana use among Whites increased from 10.7% in 2005 to 11.6-11.8% in 2009-2011 ($P<0.05$). There were no significant yearly changes in drug use prevalences among Asian-Americans, NHs/PIs, and mixed-race people; but use of any drug, especially marijuana, was prevalent among NHs/PIs and mixed-race people (21.2% and 23.3%, respectively, in 2011). Compared with Asian-Americans, NHs/PIs had higher odds of marijuana use, and mixed-race individuals had higher odds of using marijuana, cocaine, hallucinogens, stimulants, sedatives, and tranquilizers. Compared with Whites, mixed-race individuals had greater odds of any drug use, mainly marijuana, and NHs/PIs resembled Whites in odds of any drug use. Findings reveal alarmingly prevalent drug use among NHs/PIs and mixed-race people. Research on drug use is needed in these rising populations to inform prevention and treatment efforts.

The Role Of Behavioral Inhibition and Behavioral Approach Systems In the Associations Between Mood and Alcohol Consequences In College: A Longitudinal Multilevel Analysis. Wardell JD, Read JP, Colder CR. Addict Behav. 2013; 38(11): 2772-2781.
The behavioral inhibition system (BIS) and behavioral approach system (BAS) are thought to influence sensitivity to reinforcement and punishment, making them useful for predicting mood-related drinking outcomes. This study provided the first examination of BIS and BAS as moderators of longitudinal within-person associations between mood and alcohol-related consequences in college student drinkers. Participants (N = 637) at two public U.S. universities completed up to 14 online surveys over the first three years of college assessing past-month general positive and negative moods, as well as past-month alcohol use and consequences. BIS and BAS were assessed at baseline. Using multilevel regression, the authors found that BIS and BAS moderated the within-person associations between negative mood and alcohol consequences. For students high on BIS only, high on BAS only, or high on both BIS and BAS, within-person increases in negative mood were associated with greater alcohol consequences in the first year of college. However, these negative mood-alcohol consequence associations diminished over time for students high on BIS and low on BAS, but remained strong for students high on both BIS and BAS. Within-person associations between positive mood and alcohol consequences changed from slightly positive to slightly negative over time, but were not moderated by BIS or BAS. Findings suggest that BIS and BAS impact the within-person association between general changes in negative mood and negative alcohol consequences, working jointly to maintain this relationship over time.

Adolescents' Nonmedical Use and Excessive Medical Use Of Prescription Medications and The Identification Of Substance Use Subgroups. Cranford JA, McCabe SE, Boyd CJ. Addict Behav. 2013; 38(11): 2768-2771.
The purpose of this study was to identify subgroups of adolescents based on their past 12 months use of tobacco, alcohol, marijuana, illicit drugs, and nonmedical use and excessive medical use of prescription medications. A cross-sectional Web-based survey of adolescents from two middle and high school districts in Southeastern Michigan was conducted. The sample included 2,744 middle school (7th and 8th grade) and high school (9th through 12th grade) students. Participants had a mean age of 14.8 years (SD = 1.9 years); 50.4% were female, 64.1% were Caucasian, and 30.6% were African American. Participants completed measures of the past 12 months of substance use, parental monitoring, parental substance use, and internalizing and externalizing problems. Exploratory latent class analysis (LCA) indicated four classes. The largest class was composed of participants with low probabilities of using any substances (low/no use class), and the smallest class was composed of participants with relatively high probabilities of using all substances (multiple substances class). A third class included participants with high probabilities of using tobacco, alcohol, and marijuana (TAM). The fourth class consisted of participants with relatively high probabilities of alcohol use, nonmedical prescription drug use, and excessive medical use of prescription drugs (ANM). Female gender predicted membership in the ANM and multiple substance classes, and parental monitoring, parental substance use problems, internalizing, and externalizing problems uniquely predicted membership in all three high-risk risk classes. Results indicated three high-risk subgroups of adolescents, each characterized by a different pattern of substance use. Two risk groups are characterized by relatively high probabilities of nonmedical use and excessive medical use of prescription medications.

Novel Psychoactive Drug Use Among Younger Adults Involved In US Nightlife Scenes. Kelly BC, Wells BE, Pawson M, LeClair A, Parsons JT, Golub SA. Drug Alcohol Rev. 2013. The emergence of novel psychoactive substances has been reported in clinical studies and recent studies of users. The use of these substances in European nightlife scenes is well documented. Little research has been done to identify the prevalence of these drugs among young adults active in other regions. The authors focus their sample on socially active young adults to gain an indication of the prevalence and understanding of demographic factors associated with past year mephedrone ('meph', 'bath salts') and synthetic cannabinoid ('spice', 'K2') use. This study reports on the results of a field-based survey of 1740 patrons at nightlife venues in New York City. Within the sample, 8.2% reported use of synthetic cannabinoids and 1.1% reported the use of mephedrone. Gay and bisexual men reported higher prevalence of mephedrone use. Latinos reported higher prevalence of synthetic cannabinoid use. Multivariate analyses indicate that sexual minority identity is associated with mephedrone use and younger age and Latino ethnicity are associated with synthetic cannabinoid use. The findings suggest that the use of synthetic cannabinoids and mephedrone among adults in US nightlife scenes remains relatively low in comparison with European nightlife scenes, and is low relative to other drug use among young people within these scenes.

HIV Transmission From Drug Injectors To Partners Who Do Not Inject, and Beyond: Modelling The Potential For A Generalized Heterosexual Epidemic In St. Petersburg, Russia. Mills HL, White E, Colijn C, Vickerman P, Heimer R. Drug Alcohol Depend. 2013; 133(1): 242-247.
HIV infection is prevalent among drug injectors in St. Petersburg and their non-injecting heterosexual partners (PIDUs). There are fears that sexual transmission of HIV from IDUs to PIDUs may portend a self-sustaining, heterosexual epidemic in Russia. The authors' model combines a network model of sexual partnerships of IDUs and non-IDUs to represent sexual transmission of HIV and a deterministic model for parenteral transmission among IDUs. Behavioural parameters were obtained from a survey of St. Petersburg IDUs and their sexual partners. The authors based their model fits on two scenarios for PIDU prevalence in 2006 (5.6% and 15.1%, calculated excluding and including HCV co-infected PIDUs respectively) and compared predictions for the general population HIV prevalence.Results indicate that sexual transmission could sustain a non-IDU HIV epidemic. The model indicates that general population prevalence may be greater than current estimates imply. Parenteral transmission drives the epidemic and the PIDU bridge population plays a crucial role transferring infection to non-IDUs. The model indicates that the high PIDU prevalence is improbable because of the high risk behaviour this implies; the lower prevalence is possible. The model implies that transmission through PIDUs will sustain a heterosexual epidemic, if prevalence among IDUs and PIDUs is as high as survey data suggest. The authors postulate that current estimates of population prevalence underestimate the extent of the HIV epidemic because they are based on the number of registered cases only. Curtailing transmission among injectors and PIDUs will be vital in controlling heterosexual transmission.

Prevalence and Correlates Of Street-Obtained Buprenorphine Use Among Current and Former Injectors In Baltimore, Maryland. Genberg BL; Gillespie M, Schuster CR, Johanson C-E, Astemborski J, Kirk GD, Vlahov D, Mehta SH. Addict Behav. 2013; 38(12): 2868-2873.
There are few systematic assessments of street-obtained buprenorphine use from community-based samples in the United States. The objective of this study was to characterize the prevalence, correlates, and reasons for street-obtained buprenorphine use among current and former injection drug users (IDUs) in Baltimore, Maryland.In 2008, participants of the ALIVE (AIDS Linked to the IntraVenous Experience) study, a community-based cohort of IDUs, were administered a survey on buprenorphine. Street-obtained buprenorphine represented self-reported use of buprenorphine obtained from the street or a friend in the prior three months. Six hundred and two respondents were predominantly male (65%), African-American (91%), and 30% were HIV-positive. Overall, nine percent reported recent street-obtained buprenorphine use, and only 2% reported using to get high. Among active opiate users, 23% reported recent use of street-obtained buprenorphine. Use of buprenorphine prescribed by a physician, injection and non-injection drug use, use of street-obtained methadone and prescription opiates, homelessness, and opioid withdrawal symptoms were positively associated, while methadone treatment, health insurance, outpatient care, and HIV-infection were negatively associated with recent street-obtained buprenorphine use in univariate analysis. After adjustment, active injection and heroin use were positively associated with street-obtained buprenorphine use. Ninety-one percent reported using street-obtained buprenorphine to manage withdrawal symptoms. While 9% reported recent street-obtained buprenorphine use, only a small minority reported using buprenorphine to get high, with the majority reporting use to manage withdrawal sympoms. There is limited evidence of diversion of buprenorphine in this sample and efforts to expand buprenorphine treatment should continue with further monitoring.

HIV Prevalence Overall and Among High-HIV-Risk Behaviorally Defined Subgroups Among Heterosexuals At Community-Based Venues In A Mid-Atlantic, US City. Polk S, Ellen JM, Fichtenberg C, Huettner S, Jennings JM. J Urban Health. 2013; 90(4): 747-757.
A clear understanding of local transmission dynamics is a prerequisite for the design and implementation of successful HIV prevention programs. There is a tremendous need for such programs geared towards young African-American women living in American cities with syndemic HIV and injection drug use. In some of these American cities, including Baltimore, the HIV prevalence rate among young African-American women is comparable to that in some African nations. High-risk heterosexual sex, i.e., sex with an injection drug user or sex with someone known to have HIV, is the leading risk factor for these young women. Characterizing transmission dynamics among heterosexuals has been hampered by difficulty in identifying HIV cases in these settings. The case identification method described in this paper was designed to address challenges encountered by previous researchers, was based on the Priorities for Local AIDS Cases methodology, and was intended to identify a high number of HIV cases rather than achieve a representative sample (Weir et al., Sex Transm Infect 80(Suppl 2):ii63-8, 2004. Through a three-phase process, 87 venues characterized as heterosexual sex partner meeting sites were selected for participant recruitment in Baltimore, MD. One thousand six hundred forty-one participants were then recruited at these 87 venues, administered a behavioral risk questionnaire, and tested for HIV. The HIV prevalence was 3% overall, 3% among males, and 4% among females and ranged from 1.7 to 22.6% among high-HIV-risk subgroups. These findings indicate that attributing HIV transmission to high-risk heterosexual sex vs. other high-HIV-risk behaviors

would be difficult. Moving beyond individual risk profiles to characterize the risk profile of venues visited by heterosexuals at high risk of HIV acquisition may reveal targets for HIV transmission prevention and should be the focus of future investigations.

CVD Risk Among Men Participating In The National Health And Nutrition Examination Survey (NHANES) From 2001 To 2010: Differences By Sexual Minority Status. Farmer GW, Bucholz KK, Flick LH, Burroughs TE, Bowen DJ. J Epidemiol Community Health. 2013; 67(9): 772-778.
Recent research indicates that sexual minority women are at increased risk for cardiovascular disease (CVD) compared with heterosexual women; however, few studies of CVD risk exist for sexual minority men (SMM). This study aimed to determine whether disparities in CVD risk exist for SMM and if CVD risk is consistent across subgroups of SMM. This study utilized publicly available data from the National Health and Nutrition Examination Survey (NHANES), pooled from 2001 to 2010. CVD risk was calculated using the Framingham General CVD Risk Score and operationalised as the ratio of a participant's vascular and chronological age. Differences in this ratio were examined between heterosexual and SMM as a whole, and within subgroups of SMM.SMM had vascular systems that were, on average, 4% (95% CI -7.5% to -0.4%) younger than their heterosexual counterparts; however, adjustment for education and history of hard drug use rendered this difference statistically insignificant. Analysis of SMM subgroups revealed increased CVD risk for bisexual men and decreased CVD risk for both gay and homosexually experienced heterosexual men when compared with heterosexual men. Differences in CVD risk persisted for only bisexual and homosexually experienced heterosexual men after adjustment for education and history of hard drug use. Subgroups of SMM are at increased risk for CVD compared with heterosexual men, and this increased risk cannot be completely attributed to differences in demographic characteristics or negative health behaviours.

Posttraumatic Stress Disorder Symptom Clusters, Alcohol Misuse, and Women's Use Of Intimate Partner Violence. Hellmuth JC, Jaquier V, Young-Wolff K, Sullivan TP. J Trauma Stress. 2013; 26(4): 451-458.
Exploring how PTSD and alcohol misuse relate to women's use of intimate partner violence (IPV) is vital to develop our understanding of why some women may engage in IPV, which can serve to maximize intervention efforts for women. This study examined the extent to which posttraumatic stress disorder (PTSD) symptom clusters are directly and indirectly related to women's use of IPV through pathways involving alcohol misuse while controlling for severity of women's IPV victimization. The sample was comprised of substance-using, low socioeconomic status community women (N = 143) currently experiencing IPV victimization. The majority of the sample was African American (n = 115, 80.42%). This sample had an average annual household income of $14,368.68 (SD = $12,800.68) and the equivalent of a high school education (11.94 years, SD = 1.32). Path analyses indicated that the strongest statistical relationship emerged between women's use of IPV and women's IPV victimization. PTSD reexperiencing and numbing symptom severity was related to women's use of psychological, minor physical, and severe physical IPV; however, these relationships were indirect through alcohol misuse. Findings lend preliminary support for the application of the self-medication hypothesis to the study of PTSD, alcohol misuse, and IPV among women.

Coping and Emotion Regulation Profiles As Predictors Of Nonmedical Prescription Drug and Illicit Drug Use Among High-Risk Young Adults. Wong CF, Silva K, Kecojevic A, Schrager SM, Bloom JJ, Iverson E, Lankenau SE. Drug Alcohol Depend. 2013; 132(1-2): 165-171.

Deficits in the ability to organize, integrate, and modulate emotions, thoughts, and behaviors when dealing with stress have been found to be related to the onset and escalation of substance use among adolescents and young adults. However, limited research has focused on understanding how coping and emotion regulation tendencies might be associated with different patterns of prescription and illicit drug use, particularly among high-risk young adults who may already face additional challenges relative to lower-risk populations. Young adults aged 16-25 years who had misused prescription drugs within the past 90 days were interviewed in Los Angeles and New York. The current study utilized latent profile analysis to empirically derive coping and emotion regulation typologies/ profiles that are then used to predict different patterns of substance use (N=560). Four latent classes/groups were identified: (1) suppressors, (2) others-reliant copers, (3) self-reliant copers and (4) active copers. Distinct patterns of prescription and illicit drug misuse were found among different coping/emotion regulation profiles, including differences in age of initiation of opiates, tranquilizers, and illicit drugs, recent injection drug use, substance use-related problems, and past 90-day use of tranquilizers, heroin, and cocaine. Specifically, suppressors and others-reliant copers evidenced more problematic patterns of substance use compared to active copers. This is among the first studies to show how coping and emotion regulation profiles predict distinct patterns of substance use. Results provide the groundwork for additional investigations that could have significant prevention and clinical implications for substance-using high-risk young adults.

Adolescent Athletic Participation and Nonmedical Adderall Use: An Exploratory Analysis Of A Performance-Enhancing Drug. Veliz P, Boyd C, McCabe SE. J Stud Alcohol Drugs. 2013; 74(5): 714-719.

A primary motive for adolescents and young adults to nonmedically use prescription stimulants is to help them study. Adolescents and young adults are using prescription stimulants, such as Adderall (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate), as performance enhancers in certain social domains, including academics and sports. The purpose of this exploratory study was to examine the nonmedical use of Adderall (a commonly prescribed stimulant used nonmedically) among adolescents who participate in competitive sports. The Monitoring the Future survey for 2010 and 2011, a representative sample of 8th- and 10th-grade students, surveyed involvement in competitive sports and nonmedical Adderall use among 21,137 adolescents. Past-year nonmedical use of Adderall served as the main outcome measure. Logistic regression analyses were run to examine whether sports participation in general and involvement in different types of competitive sports participation were associated with past-year nonmedical use of Adderall among males and females. The odds of past-year nonmedical use of Adderall among males were higher for male respondents who participated in lacrosse (adjusted odds ratio [AOR] = 2.52, 95% CI [1.20, 5.29]) and wrestling (AOR = 1.74, 95% CI [1.01, 2.98]). However, no particular sport among females was found to be associated with past-year nonmedical use of Adderall. Certain extracurricular activities, such as high-contact sports, may influence male participants to misuse prescription stimulants as performance enhancers either on or off the playing field.

False Identification Use Among College Students Increases The Risk For Alcohol Use Disorder: Results Of A Longitudinal Study. Arria AM, Caldeira KM, Vincent KB, Bugbee BA, O'Grady KE. Alcohol Clin Exp Res. 2013.

It is well known that using false identification (ID) is a common method by which underage youth in the United States obtain alcohol. While false ID use is associated with high-risk drinking patterns, its association with alcohol use disorder (AUD), independent of other risk factors, has not been firmly established. Participants were 1,015 college students recruited from 1 university and assessed annually during their first 4years of college. Latent variable growth curve modeling was used to identify significant predictors of false ID use and test the hypothesis that false ID use increased the risk for AUD, by increasing the frequency and/or quantity of alcohol use. Several other hypothesized risk factors for AUD were accounted for, including demographics (sex, race, living situation, religiosity, socioeconomic status), individual characteristics (childhood conduct problems, sensation-seeking, age at first drink), high school behaviors (high school drinking frequency, drug use), family factors (parental monitoring, parental alcohol problems), perception of peer drinking norms, and other factors related to false ID use.False IDs were used by almost two-thirds (66.1%) of the sample. False ID use frequency was positively associated with baseline quantity and frequency of alcohol use, independent of all other factors tested. False ID use was not directly related to AUD risk, but indirectly predicted increases in AUD risk over time through its association with greater increases in alcohol use frequency over time. Several predictors of false ID use frequency were also identified.False ID use may contribute to AUD risk by facilitating more frequent drinking. If replicated, these findings highlight the potential public health significance of policies that enforce sanctions against false ID use. Students who use false IDs represent an important target population for alcohol prevention activities.

Antiretroviral Medication: An Emerging Category Of Prescription Drug Misuse. Davis GP, Surratt HL, Levin FR, Blanco C. Am J Addict. 2013.

Prescription drug abuse has been a focus of public health concern over the past two decades with many studies addressing patterns of narcotic analgesic abuse and diversion. Most research in this domain has centered on controlled substances with known abuse liability. However, the scientific literature has been virtually silent regarding other prescribed medications with previously undocumented addictive potential, such as antiretroviral (ARV) medications for treatment of human immunodeficiency virus. This article reviews the available evidence that suggests a growing problem of ARV diversion and abuse and explores the reasons for the misuse of these medications based on the theoretical neuropsychiatric effects of ARVs and the drug-drug interactions between ARVs and other drugs of abuse. Review of media reports and qualitative studies suggest that ARV medications are emerging drugs of abuse. Claims about the psychoactive effects of ARV medications are supported by scientific case reports. This article reviews the evidence to date of an emerging problem of diversion and misuse of ARV medications for recreational purposes. Implications of ARV misuse and diversion are discussed with suggestions for future research and intervention.

Developmental Trajectories Of Alcohol Use Among Monoracial and Biracial Black Adolescents and Adults. Blacks. Clark TT, Corneille M, Coman E. J Psychoactive Drugs. 2013; 45(3): 249-257.
The present study investigates developmental trajectories of alcohol use from early adolescence to adulthood by age and race/ethnicity among White, Black, Black-American Indian, Black-Hispanic, and Black-White individuals and associated sociodemograhphic correlates. The authors used a subsample of nationally representative data obtained from the National Longitudinal Study of Adolescent Health (Add Health). The analytic sample consisted of 15,278 individuals in Wave 1 (ages 11 to 21 years). The sample consists of adolescents who were in Grades 7-12 at wave one and who were followed across four waves of data collection into adulthood. Respondents could report more than one race/ethnicity. The authors find distinct alcohol trajectories among monoracial and biracial/ethnic Blacks with all groups showing a cross-over or catch-up effect. Black-White adults demonstrated a cross-over effect by surpassing the alcohol drinking rates of Whites in adulthood, Black-American Indians showed a within-group catch-up effect by surpassing the alcohol drinking rates of monoracial and biracial/ethnic Blacks in adulthood, and monoracial Blacks were most likely to be non-drinkers in adulthood. The authors also show gender, socioeconomic status, and household structure differences in impact on alcohol use among monoracial and biracial/ethnic Blacks. Significant heterogeneity is observed regarding alcohol trajectories between monoracial and biracial/ethnic Blacks.

Functional Imaging Of Implicit Marijuana Associations During Performance On An Implicit Association Test (IAT). L Ames, Susan; Grenard, Jerry L; W Stacy, Alan; Xiao, Lin; He, Qinghua; Wong, Savio W; Xue, Gui; W Wiers, Reinout; Bechara, Antoine Behav Brain Res. 2013; 256: 494-502. (CHECK AUTHORS)
This research evaluated the neural correlates of implicit associative memory processes (habit-based processes) through the imaging (fMRI) of a marijuana Implicit Association Test. Drug-related associative memory effects have been shown to consistently predict level of drug use. To observe differences in neural activity of associative memory effects, this study compared 13 heavy marijuana users and 15 non-using controls, ranging in age from 18 to 25, during performance of a marijuana Implicit Association Test (IAT). Group by condition interactions in the putamen, caudate, and right inferior frontal gyrus were observed. Relative to non-users, marijuana users showed greater bilateral activity in the dorsal striatum (caudate and putamen) during compatible trials focused on perceived positive outcomes of use. Alternatively, relative to the marijuana-using group, the non-users showed greater activity in the right inferior frontal gyrus during incompatible trials, which require more effortful processing of information. Further, relative to fixation, heavy users showed bilateral activity in the caudate and putamen, hippocampus and some frontal regions during compatible trials and no significant activity during incompatible trials. The non-using group showed greater activity in frontal regions during incompatible trials relative to fixation and no significant activity during compatible trials. These findings are consistent with a dual process framework of appetitive behaviors proposing that (1) implicit associations underlying habit are mediated through neural circuitry dependent on the striatum, and (2) deliberative/controlled behaviors are mediated through circuitry more dependent on the prefrontal cortex.

Correlates Of Elevated Interleukin-6 and C-Reactive Protein In Persons With Or At High-Risk For HCV and HIV Infections. Salter ML, Lau B, Mehta SH, Go VF, Leng S, Kirk GD. J Acquir Immune Defic Syndr. 2013.
HIV and HCV infections may increase interleukin-6 (IL-6) and C-reactive protein (CRP). However, relationships between inflammatory biomarkers, chronic viral infections, clinical factors, and behavioral factors remain poorly understood. Using linear regression, the authors modeled cross-sectional associations between loge IL-6 or loge CRP levels and HCV, HIV, injection drug use, and comorbidity among 1191 injection drug users. Mean age was 47 years, 46.0% reported currently injecting drugs, 59.0% were HCV-monoinfected, and 27% were HCV/HIV-coinfected. In multivariable models, higher loge IL-6 was associated with HCV monoinfection (=0.191, 95%CI: 0.043 to 0.339) and HCV/HIV coinfection (=0.394, 95% CI: 0.214 to 0.574). In contrast, HCV monoinfection (=-0.523, 95%CI: -0.275 to -0.789) and HCV/HIV coinfection (=-0.554 95%CI: -0.260 to -0.847) were associated with lower CRP. Lower CRP with HCV infection was independent of liver fibrosis severity, synthetic function, or liver injury markers; CRP decreased with higher HCV RNA. Increased injection intensity was associated with higher IL-6 ($p=0.003$) and CRP ($p<0.001$); increasing comorbidity ($p<0.001$) and older age ($p=0.028$) were associated with higher IL-6; older age was associated with higher CRP among HCV-uninfected participants ($p=0.021$). HIV and HCV infections contribute to chronic inflammation; however, reduced CRP possibly occurs through HCV-virally-mediated mechanisms. Findings highlight potentially modifiable contributors to inflammation.

Dynamics Of Viral Evolution and Neutralizing Antibody Response After HIV-1 Superinfection. Chaillon A, Wagner GA, Hepler N L, Little SJ, Kosakovsky Pond SL, Caballero G, Pacold ME, Phung P, Wrin T, Richman DD, Wertheim JO, Smith DM. J Virol. 2013; 87(23): 12737-12744.
Investigating the incidence and prevalence of HIV-1 superinfection is challenging due to the complex dynamics of two infecting strains. The superinfecting strain can replace the initial strain, be transiently expressed, or persist along with the initial strain in distinct or in recombined forms. Various selective pressures influence these alternative scenarios in different HIV-1 coding regions. The authors hypothesized that the potency of the neutralizing antibody (NAb) response to autologous viruses would modulate viral dynamics in env following superinfection in a limited set of superinfection cases. HIV-1 env pyrosequencing data were generated from blood plasma collected from 7 individuals with evidence of superinfection. Viral variants within each patient were screened for recombination, and viral dynamics were evaluated using nucleotide diversity. NAb responses to autologous viruses were evaluated before and after superinfection. In 4 individuals, the superinfecting strain replaced the original strain. In 2 individuals, both initial and superinfecting strains continued to cocirculate. In the final individual, the surviving lineage was the product of interstrain recombination. NAb responses to autologous viruses that were detected within the first 2 years of HIV-1 infection were weak or absent for 6 of the 7 recently infected individuals at the time of and shortly following superinfection. These 6 individuals had detectable on-going viral replication of distinct superinfecting virus in the env coding region. In the remaining case, there was an early and strong autologous NAb response, which was associated with extensive recombination in env between initial and superinfecting strains. This extensive recombination made superinfection more difficult to identify and may explain why the detection of superinfection has typically been associated with low autologous NAb titers.

Hepatitis C Viremia and The Risk Of Chronic Kidney Disease In HIV-Infected Individuals. Lucas GM, Jing Y, Sulkowski M, Abraham AG, Estrella MM, Atta MG, Fine DM, Klein MB, Silverberg MJ, Gill MJ, Moore RD, Gebo KA, Sterling TR, Butt AA; NA-ACCORD of the IeDEA. J Infect Dis. 2013; 208(8): 1240-1249.
The role of active hepatitis C virus (HCV) replication in chronic kidney disease (CKD) risk has not been clarified. The authors compared CKD incidence in a large cohort of HIV-infected subjects who were HCV seronegative, HCV viremic (detectable HCV RNA), or HCV aviremic (HCV seropositive, undetectable HCV RNA). Stages 3 and 5 CKD were defined according to standard criteria. Progressive CKD was defined as a sustained 25% glomerular filtration rate (GFR) decrease from baseline to a GFR < 60 mL/min/1.73 m2. The authors used Cox models to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). A total of 52 602 HCV seronegative, 9508 HCV viremic, and 913 HCV aviremic subjects were included. Compared with HCV seronegative subjects, HCV viremic subjects were at increased risk for stage 3 CKD (adjusted HR 1.36 [95% CI, 1.26, 1.46]), stage 5 CKD (1.95 [1.64, 2.31]), and progressive CKD (1.31 [1.19, 1.44]), while HCV aviremic subjects were also at increased risk for stage 3 CKD (1.19 [0.98, 1.45]), stage 5 CKD (1.69 [1.07, 2.65]), and progressive CKD (1.31 [1.02, 1.68]). Compared with HIV-infected subjects who were HCV seronegative, both HCV viremic and HCV aviremic individuals were at increased risk for moderate and advanced CKD.

Selection and Influence Mechanisms Associated With Marijuana Initiation and Use In Adolescent Friendship Networks. de la Haye K, Green Jr, HD, Kennedy DP, Pollard MS, Tucker JS. J Res Adolesc. 2013; 23(3).
Friends are thought to influence adolescent drug use. However, few studies have examined the role of drugs in friendship selection, which is necessary to draw sound conclusions about influence. This study applied statistical models for social networks to test the contribution of selection and influence to associations in marijuana use among friends in two large high schools (N = 1,612; M age = 16.4). There was evidence for friend selection based on similar lifetime and current marijuana use at both schools, but friends were found to influence the initiation and frequency of adolescent marijuana use in just one of these schools. There was minimal evidence that peer effects were moderated by personal, school, or family risk factors.

Clostridium Difficile In A HIV-Infected Cohort: Incidence, Risk Factors, and Clinical Outcomes. Haines CF, Moore RD, Bartlett JG, Sears CL, Cosgrove SE, Carroll K, Gebo KA. AIDS. 2013.
C. difficile is the most commonly reported infectious diarrhea in HIV-infected patients in the United States. The authors set out to determine the incidence, risk factors, and clinical presentation of C. difficile infections (CDI) in a cohort of HIV-infected subjects. They performed a nested, case-control analysis with four non-CDI controls randomly selected for each case. They assessed the incidence of CDI in the Johns Hopkins HIV Clinical Cohort between July 1, 2003 and December 31, 2010. Incident cases were defined as first positive C. difficile cytotoxin assay or PCR for toxin B gene. The authors used conditional logistic regression models to assess risk factors for CDI. They abstracted data on the clinical presentation and outcomes from case chart review. They identified 154 incident CDI cases for an incidence of 8.3 cases/1000 patient years. No unique clinical features of HIV-associated CDI were identified. In multivariate analysis, risk of CDI was independently increased for: CD4 count 50 cells/mm (Adjusted Odds Ratio (AOR) 20.7, 95% CI 2.8-151.4), hospital onset CDI (AOR 26.7 [3.1-

231.2]), and use of clindamycin (AOR 27.6 [2.2-339.4]), fluoroquinolones (AOR 4.5 [1.2-17.5]), macrolides (AOR 6.3 [1.8-22.1]), gastric acid suppressants (AOR 3.1 [1.4-6.9]), or immunosuppressive agents (AOR 6.8 [1.2-39.6]). The incidence of CDI in HIV-infected patients was twice that previously reported. These data show compromised cellular immunity, as defined by CD4 50 cells/mm, is a risk factor for CDI. Clinicians should be aware of the increased CDI risk, particularly in those with severe CD4 count suppression.

Cumulative and Recent Psychiatric Symptoms As Predictors Of Substance Use Onset: Does Timing Matter? Cerda M, Bordelois PM, Keyes KM, Galea S, Koenen KC, Pardini D. Addiction. 2013.
The authors examined two questions about the relationship between conduct disorder (CD), depression and anxiety symptoms and substance use onset: (i) what is the relative influence of recent and more chronic psychiatric symptoms on alcohol and marijuana use initiation and (ii) are there sensitive developmental periods when psychiatric symptoms have a stronger influence on substance use initiation? Secondary analysis of longitudinal data from the Pittsburgh Youth Study, a cohort study of boys followed annually from 7 to 19 years of age. Recruitment occurred in public schools in Pittsburgh, Pennsylvania, USA. A total of 503 boys were studied. The primary outcomes were age of alcohol and marijuana use onset. Discrete-time hazard models were used to determine whether (i) recent (prior year); and (ii) cumulative (from age 7 until 2 years prior to substance use onset) psychiatric symptoms were associated with substance use onset. Recent anxiety symptoms [hazard ratio (HR)=1.10, 95% confidence interval (CI)=1.03-1.17], recent (HR=1.59, 95% CI=1.35-1.87), cumulative (HR=1.45, 95% CI=1.03-2.03) CD symptoms, and cumulative depression symptoms (HR=1.04, 95% CI=1.01-1.08) were associated with earlier alcohol use onset. Recent (HR=1.39, 95% CI=1.22-1.58) and cumulative CD symptoms (HR=1.38, 95% CI=1.02-1.85) were associated with marijuana use onset. Recent anxiety symptoms were only associated with alcohol use onset among black participants. Timing matters in the relationship between psychiatric symptoms and substance use onset in childhood and adolescence, and the psychiatric predictors of onset are substance-specific. There is no single sensitive developmental period for the influence of psychiatric symptoms on alcohol and marijuana use initiation.

Mental Disorders and Risk Of Accidental Death. Crump C, Sundquist K, Winkleby MA, Sundquist J. Br J Psychiatry. 2013; 203: 297-302.
Little is known about accidental death risks among psychiatric patients. The objective of Jennings JM, Woods SE, Curriero FC. Health Place. 2013; 23: 128-137. this study was to examine this issue in the most comprehensive study to date. This was a National cohort study of all Swedish adults (n = 6,908,922) in 2001-2008. There were 22,419 (0.3%) accidental deaths in the total population, including 5933 (0.9%) accidental deaths v. 3731 (0.6%) suicides among psychiatric patients (n = 649,051). Of persons who died from accidents, 26.0% had any psychiatric diagnosis v. 9.4% in the general population. Accidental death risk was four- to sevenfold among personality disorders, six- to sevenfold among dementia, and two- to fourfold among schizophrenia, bipolar disorder, depression or anxiety disorders, and was not fully explained by comorbid substance use. Strong associations were found irrespective of sociodemographic characteristics, and for different types of accidental death (especially poisoning or falls). All mental disorders were strong independent risk factors for accidental death, which was substantially more common than suicide.

Navigating the Risk Environment: Structural Vulnerability, Sex, and Reciprocity Among Women Who Use Methamphetamine. McKenna SA. Int J Drug Policy. 2013.
Drug users' risk sexual practices contribute to their increased risk for contracting HIV and other sexually transmitted infections. Use of methamphetamine has been associated with a number of high-risk sexual practices such as frequent sexual contacts, multiple sex partners, unprotected sex, and exchange sex. The media construct women who use methamphetamine as engaging in exchange sex to support their drug habit. Despite an abundance of data on exchange sex among heroin and crack users that suggest the importance of examining these practices in context, they remain understudied among female methamphetamine users. This article draws on ongoing ethnographic research with female methamphetamine users.The research participants' risk environment(s) contribute to their structural vulnerability and shape behaviour in ways that are sometimes deemed transactional and risky by research, public health, or harm reduction professionals. Understanding the embededdness of sexual practices in structural context and networks of reciprocity is essential to understanding implications for policy and harm reduction.

PREVENTION RESEARCH

Opening The "Black Box": Family Check-Up Intervention Effects On Self-Regulation That Prevents Growth In Problem Behavior and Substance Use. Fosco GM, Frank JL, Stormshak EA, Dishion TJ. J Sch Psychol. 2013; 51(4): 455-468.
Family-school interventions are a well-established method for preventing and remediating behavior problems in at-risk youth, yet the mechanisms of change underlying their effectiveness are often overlooked or poorly understood. The Family Check-Up (FCU), a school-based, family-centered intervention, has been consistently associated with reductions in youth antisocial behavior, deviant peer group affiliation, and substance use. The purpose of this study was to explore proximal changes in student-level behavior that accounts for links between implementation of the FCU and changes in youth problem behavior. Data were drawn from a randomized controlled trial study of the efficacy of the FCU among 593 ethnically diverse middle school students followed longitudinally from 6th through 8th grades. Latent growth curve analyses revealed that random assignment to the FCU intervention condition was related to increased mean levels of students' self-regulation from 6th to 7th grades, which in turn reduced the risk for growth in antisocial behavior, involvement with deviant peers, and alcohol, tobacco, and marijuana use through the 8th grade. Overall, these findings highlight the robust implications of self-regulation as a proximal target for family-centered interventions.

Using Genetically Informed, Randomized Prevention Trials To Test Etiological Hypotheses About Child and Adolescent Drug Use and Psychopathology. Brody GH, Beach SRH, Hill KG, Howe GW, Prado G, Fullerton SM. Am J Public Health. 2013; 103 Suppl 1: S19-24.
In this essay, the authors describe a new era of public health research in which prevention science principles are combined with genomic science to produce gene-intervention (G-I) research. They note the roles of behavioral and molecular genetics in risk and protective mechanisms for drug use and psychopathology among children and adolescents, and the results of first-generation genetically informed prevention trials are reviewed. They also consider the need for second-generation research that focuses on G-I effects on mediators or intermediate processes. This research can be used to further understanding of etiological processes, to identify individual differences in children's and adolescents' responses to risk, and to increase the precision of prevention programs. The authors note the caveats about using genetic data to select intervention participants.

The Predictive Utility Of A Brief Kindergarten Screening Measure Of Child Behavior Problems. Racz SJ, King KM, Wu J, Witkiewitz K, McMahon RJ. J Consult Clin Psychol. 2013; 81(4): 588-599.
Kindergarten teacher ratings, such as those from the Teacher Observation of Classroom Adaptation-Revised (TOCA-R), are a promising cost- and time-effective screening method to identify children at risk for later problems. Previous research with the TOCA-R has been mainly limited to outcomes in a single domain measured during elementary school. The goal of the current study was to examine the ability of TOCA-R sum scores to predict outcomes in multiple domains across distinct developmental periods (i.e., late childhood, middle adolescence, late adolescence). The authors used data from the Fast Track Project, a large multisite study with children at risk for conduct problems (n = 752; M age at start of study = 6.55 years; 57.7% male; 49.9% Caucasian, 46.3% African American). Kindergarten TOCA-R sum scores were used as

the predictor in regression analyses; outcomes included school difficulties, externalizing diagnoses and symptom counts, and substance use. TOCA-R sum scores predicted school outcomes at all time points, diagnosis of ADHD in 9th grade, several externalizing disorder symptom counts, and cigarette use in 12th grade. The findings demonstrate the predictive utility of the TOCA-R when examining outcomes within the school setting. Therefore, these results suggest the 10-item TOCA-R may provide a quick and accurate screening of children at risk for later problems. Implications for prevention and intervention programs are discussed.

Prevention System Mediation of Communities That Care Effects on Youth Outcomes. Brown EC, Hawkins JD, Rhew IC, Shapiro VB, Abbott RD, Oesterle S, Arthur MW, Briney JS, Catalano RF. Prev Sci. 2013.
This study examined whether the significant intervention effects of the Communities That Care (CTC) prevention system on youth problem behaviors observed in a panel of eighth-grade students (Hawkins et al. Archives of Pediatrics and Adolescent Medicine 163:789-798 2009) were mediated by community-level prevention system constructs posited in the CTC theory of change. Potential prevention system constructs included the community's degree of (a) adoption of a science-based approach to prevention, (b) collaboration on prevention activities, (c) support for prevention, and (d) norms against adolescent drug use as reported by key community leaders in 24 communities. Higher levels of community adoption of a science-based approach to prevention and support for prevention in 2004 predicted significantly lower levels of youth problem behaviors in 2007, and higher levels of community norms against adolescent drug use predicted lower levels of youth drug use in 2007. Effects of the CTC intervention on youth problem behaviors by the end of eighth grade were mediated fully by community adoption of a science-based approach to prevention. No other significant mediated effects were found. Results support CTC's theory of change that encourages communities to adopt a science-based approach to prevention as a primary mechanism for improving youth outcomes.

Effects Of PROSPER On the Influence Potential Of Prosocial Versus Antisocial Youth In Adolescent Friendship Networks. Osgood DW, Feinberg ME, Gest SD, Moody J, Ragan DT, Spoth R, Greenberg M, Redmond C. J Adolesc Health. 2013; 53(2): 174-179.
The authors test the hypothesis that an evidence-based preventive intervention will change adolescent friendship networks to reduce the potential for peer influence toward antisocial behavior. Altering adolescents' friendship networks in this way is a promising avenue for achieving setting-level prevention benefits such as expanding the reach and durability of program effects. Beginning in 2002, the Promoting School-University Partnerships to Enhance Resilience (PROSPER) randomized control trial assigned two entire sixth-grade cohorts of 14 rural and small town school districts in Iowa and Pennsylvania to receive the intervention and of 14 to control. A family-based intervention was offered in sixth grade and a school-based intervention was provided in seventh grade. More than 11,000 respondents provided five waves of data on friendship networks, attitudes, and behavior in sixth through ninth grade. Antisocial influence potential was measured by the association between network centrality and problem behavior for each of 256 networks (time, grade cohort, and school specific). The intervention had a beneficial impact on antisocial influence potential of adolescents' friendship networks, with $p < .05$ for both of the primary composite measures. Current evidence-based preventive interventions can alter adolescents' friendship networks in ways that reduce the potential for peer influence toward antisocial behavior.

Mindfulness Training Improves Attentional Task Performance In Incarcerated Youth: A Group Randomized Controlled Intervention Trial. Leonard N, Jha A, Casarjian B, Goolsarran M, Garcia C, Cleland C, Gwadz M, Massey Z. Front. Psychol. 2013; 4(792).
The authors investigated the impact of cognitive behavioral therapy and mindfulness training (CBT/MT) on attentional task performance in incarcerated adolescents. Attention is a cognitive system necessary for managing cognitive demands and regulating emotions. Yet persistent and intensive demands, such as those experienced during high-stress intervals like incarceration and the events leading to incarceration, may deplete attention resulting in cognitive failures, emotional disturbances, and impulsive behavior. The authors hypothesized that CBT/MT may mitigate these deleterious effects of high stress and protect against degradation in attention over the high-stress interval of incarceration. Using a quasi-experimental, group randomized controlled trial design, they randomly assigned dormitories of incarcerated youth, ages 16–18, to a CBT/MT intervention (youth $n = 147$) or an active control intervention (youth $n = 117$). Both arms received approximately 750 min of intervention in a small-group setting over a 3–5 week period. Youth in the CBT/MT arm also logged the amount of out-of-session time spent practicing MT exercises. The Attention Network Test was used to index attentional task performance at baseline and 4 months post-baseline. Overall, task performance degraded over time in all participants. The magnitude of performance degradation was significantly less in the CBT/MT vs. control arm. Further, within the CBT/MT arm, performance degraded over time in those with no outside-of-class practice time, but remained stable over time in those who practiced mindfulness exercises outside of the session meetings. Thus, these findings suggest that sufficient CBT/MT practice may protect against functional attentional impairments associated with high-stress intervals.

Intervention Effects on Health-Risking Sexual Behavior Among Girls in Foster Care: The Role of Placement Disruption and Tobacco and Marijuana Use. Kim HK, Pears KC, Leve LD, Chamberlain PC, Smith DK. J Child Adolesc Subst Abuse. 2013; 22(5): 370-387.
The present study examined the effects of the Middle School Success intervention (MSS), a program to promote healthy adjustment in foster girls, on their health-risking sexual behavior, using a randomized controlled trial (RCT) design. As hypothesized, girls in the intervention condition (n = 48) showed significantly lower levels of health-risking sexual behavior than did girls in the control condition (n = 52) at 36 months postbaseline. Further path analysis indicated that this intervention effect was fully mediated through its effects on girls' tobacco and marijuana use. Findings highlight the importance of providing preventive intervention services to foster girls during early adolescence.

Is Resilience Only Skin Deep?: Rural African Americans' Socioeconomic Status-Related Risk and Competence In Preadolescence and Psychological Adjustment and Allostatic Load At Age 19. Brody GH, Yu T, Chen E, Miller GE, Kogan SM, Beach SRH. Psychol Sci. 2013; 24(7): 1285-1293.
Many African American youth may develop high levels of allostatic load, a measure of physiological wear and tear on the body, by developing psychosocial competence under conditions of high risk related to socioeconomic status (SES). The current study was designed to test this hypothesis, which is based on John Henryism theory. In a representative sample of 489 African American youth living in the rural South, cumulative SES-related risks and teacher-reported competence were assessed at ages 11 to 13; depressive symptoms, externalizing

behavior, and allostatic load were assessed at age 19. The data revealed that rural African American preadolescents who evinced high psychosocial competence under conditions of high cumulative SES-related risk displayed low levels of adjustment problems along with high allostatic load at age 19. These results suggest that, for many rural African Americans, resilience may indeed be only "skin deep."

Gene Variants Associated With Antisocial Behaviour: A Latent Variable Approach. Bentley MJ, Lin H, Fernandez TV, Lee M, Yrigollen CM, Pakstis AJ, Katsovich L, Olds DL, Grigorenko EL, Leckman JF. J Child Psychol Psychiatry. 2013; 54(10): 1074-1085.
The aim of this study was to determine if a latent variable approach might be useful in identifying shared variance across genetic risk alleles that is associated with antisocial behaviour at age 15 years. Using a conventional latent variable approach, the authors derived an antisocial phenotype in 328 adolescents utilizing data from a 15-year follow-up of a randomized trial of a prenatal and infancy nurse-home visitation programme in Elmira, New York. They then investigated, via a novel latent variable approach, 450 informative genetic polymorphisms in 71 genes previously associated with antisocial behaviour, drug use, affiliative behaviours and stress response in 241 consenting individuals for whom DNA was available. Haplotype and Pathway analyses were also performed. Eight single-nucleotide polymorphisms (SNPs) from eight genes contributed to the latent genetic variable that in turn accounted for 16.0% of the variance within the latent antisocial phenotype. The number of risk alleles was linearly related to the latent antisocial variable scores. Haplotypes that included the putative risk alleles for all eight genes were also associated with higher latent antisocial variable scores. In addition, 33 SNPs from 63 of the remaining genes were also significant when added to the final model. Many of these genes interact on a molecular level, forming molecular networks. The results support a role for genes related to dopamine, norepinephrine, serotonin, glutamate, opioid and cholinergic signalling as well as stress response pathways in mediating susceptibility to antisocial behaviour. This preliminary study supports use of relevant behavioural indicators and latent variable approaches to study the potential ‘co-action’ of gene variants associated with antisocial behaviour. It also underscores the cumulative relevance of common genetic variants for understanding the aetiology of complex behaviour. If replicated in future studies, this approach may allow the identification of a ‘shared’ variance across genetic risk alleles associated with complex neuropsychiatric dimensional phenotypes using relatively small numbers of well-characterized research participants.

Substance-Use Disorders and Poverty as Prospective Predictors of First-Time Homelessness in the United States. Thompson Jr, RG, Wall MM, Greenstein E, Grant BF, Hasin DS. Am J Public Health. 2013.
The authors examined whether substance-use disorders and poverty predicted first-time homelessness over 3 years. They analyzed longitudinal data from waves 1 (2001-2002) and 2 (2004-2005) of the National Epidemiologic Survey on Alcohol and Related Conditions to determine the main and interactive effects of wave 1 substance use disorders and poverty on first-time homelessness by wave 2, among those who were never homeless at wave 1 (n=30,558). First-time homelessness was defined as having no regular place to live or having to live with others for 1 month or more as a result of having no place of one’s own since wave 1. Alcohol-use disorders (adjusted odds ratio [AOR]=1.34), drug-use disorders (AOR=2.51), and poverty (AOR=1.34) independently increased prospective risk for first-time homelessness, after

adjustment for ecological variables. Substance-use disorders and poverty interacted to differentially influence risk for first-time homelessness (P<.05), before, but not after, adjustment for controls. This study reinforces the importance of both substance-use disorders and poverty in the risk for first-time homelessness, and can serve as a benchmark for future studies. Substance abuse treatment should address financial status and risk of future homelessness.

Indicated Prevention For College Student Marijuana Use: A Randomized Controlled Trial. Lee CM, Kilmer JR, Neighbors C, Atkins DC, Zheng C, Walker DD, Larimer ME.. J Consult Clin Psychol. 2013; 81(4):702-709.
Marijuana is the most frequently reported illicit substance used on college campuses. Despite the prevalence, few published intervention studies have focused specifically on addressing high-risk marijuana use on college campuses. The present study evaluated the efficacy of an in-person brief motivational enhancement intervention for reducing marijuana use and related consequences among frequently using college students. Participants included 212 college students from 2 campuses who reported frequent marijuana use (i.e., using marijuana at least 5 times in the past month). Participants completed Web-based screening and baseline assessments and upon completion of the baseline survey were randomized to either an in-person brief intervention or an assessment control group. Follow-up assessments were completed approximately 3 and 6 months post-baseline. Marijuana use was measured by number of days used in the past 30 days, typical number of joints used in a typical week in the last 60 days, and marijuana-related consequences. Results indicated significant intervention effects on number of joints smoked in a typical week and a trend toward fewer marijuana-related consequences compared with the control group at 3-month follow-up. This study provides preliminary data on short-term effects of a focused marijuana intervention for college students at reducing marijuana use during the academic quarter.

Cigarette Prices In Military Retail: A Review and Proposal For Advancing Military Health Policy. Haddock CK, Jahnke SA, Poston WSC, Williams LN. Mil Med. 2013; 178(5): 563-569.
Tobacco use is the leading cause of preventable death in the United States and has been shown to significantly harm the combat readiness of military personnel. Unfortunately, recent research showed that cigarettes are sold at substantial discounts in military retail outlets. In fact, the military is the only retailer that consistently loses money on tobacco. Cheap tobacco prices have been identified by enlisted personnel and Department of Defense health policy experts as promoting a culture of tobacco use in the U.S. Military. This article provides an analysis of why current military tobacco pricing policy has failed to eliminate cheap tobacco prices as an incentive for use. A rationale for increasing tobacco prices also is presented along with recommendations for improved military tobacco control policy.

Addressing Core Challenges for the Next Generation of Type 2 Translation Research and Systems: The Translation Science to Population Impact (TSci Impact) Framework. Spoth R, Rohrbach LA, Greenberg M, Leaf P, Brown CH, Fagan A, Catalano RF, Pentz MA, Sloboda Z, Hawkins JD, Society for Prevention Research Type 2 Translational Task Force Members and Contributing Authors Prev Sci. 2013; 14(4): 319-351.
Evidence-based preventive interventions developed over the past two decades represent great potential for enhancing public health and well-being. Research confirming the limited extent to which these interventions have been broadly and effectively implemented, however, indicates

much progress is needed to achieve population-level impact. In part, progress requires Type 2 translation research that investigates the complex processes and systems through which evidence-based interventions are adopted, implemented, and sustained on a large scale, with a strong orientation toward devising empirically-driven strategies for increasing their population impact. In this article, the authors address two core challenges to the advancement of T2 translation research: (1) building infrastructure and capacity to support systems-oriented scaling up of evidence-based interventions, with well-integrated practice-oriented T2 research, and (2) developing an agenda and improving research methods for advancing T2 translation science. The authors also summarize a heuristic "Translation Science to Population Impact (TSci Impact) Framework." It articulates key considerations in addressing the core challenges, with three components that represent: (1) four phases of translation functions to be investigated (pre-adoption, adoption, implementation, and sustainability); (2) the multiple contexts in which translation occurs, ranging from community to national levels; and (3) necessary practice and research infrastructure supports. Discussion of the framework addresses the critical roles of practitioner-scientist partnerships and networks, governmental agencies and policies at all levels, plus financing partnerships and structures, all required for both infrastructure development and advances in the science. The article concludes with two sets of recommended action steps that could provide impetus for advancing the next generation of T2 translation science and, in turn, potentially enhance the health and well-being of subsequent generations of youth and families.

Measuring Collective Efficacy Among Children In Community-Based Afterschool Programs: Exploring Pathways Toward Prevention and Positive Youth Development.
Smith EP, Osgood DW, Caldwell L, Hynes K, Perkins DF. Am J Community Psychol. 2013; 52(1-2): 27-40.
Collective efficacy refers to a perceived sense of connectedness and willingness to intervene among youth, and is a potential aspect of positive youth development (Larson in Am Psychol 55:170-183, 2000; Lerner et al. in Child Dev 71:11-20, 2000; Sampson et al. in Science 277:918-924, 1997). Theoretically, those who feel connected to a group that is empowered to positively influence the behavior of their peers may demonstrate fewer problem behaviors. Few studies, however, have measured the impact of youth perceptions of collective efficacy. As a relatively new child-related research topic, there is much to be learned. One contribution to the foundation of this research agenda begins by evaluating the reliability and validity of a measure of collective efficacy with elementary children attending community-based afterschool programs. This paper describes the internal consistency reliability and various indicators of construct and concurrent validity of the Collective Efficacy Among Children Scale. The measure was found to have high internal consistency reliability. Construct validity was tested using exploratory factor analyses of collective efficacy including the dimensions of willingness to intervene and cohesion found in previous research (Sampson et al. in Science 277:918-924, 1997). Concurrent validity assessed relations between the scale and other measures in theoretically congruent ways. Using Hierarchical Linear Models to account for children's nestedness in after-school programs, connectedness was found to be more related to emotional adjustment, particularly children's prosocial attitudes (caring about others and sharing). Children's perception of the willingness of the group to intervene was found to be related to less problem behavior, (i.e. smoking tobacco, drinking alcohol, vandalism, and stealing). The implications suggest that future research should further explore children's collective efficacy, and ways to foster its development in youth-serving afterschool settings.

Sexual Risk Behavior and STI Health Literacy Among Ethnic Minority Adolescent Women. Dimmitt Champion J, Harlin B, Collins JL.Appl Nurs Res. 2013 Nov; 26(4): 204-209.
Although information is available for prevention of sexually transmitted infection (STI/HIV), adolescents continue to engage in high risk sexual behavior particularly ethnic minority adolescent women with histories of STI or abuse. A description therefore of STI/HIV knowledge and sexual risk behavior among these women is indicated for modification of prevention efforts for sexual health promotion. African-American (n=94) and Mexican-American (n=465) adolescent women 14-18years of age were included in the study. Assessments of sexual risk behavior and STI/HIV knowledge among these adolescent women described Mexican-American women as at higher risk of STI, pregnancy, substance use and abuse with lower levels of STI/HIV knowledge, previous HIV testing and perceptions of risk than African-American women. A focus on Mexican-American adolescent women with histories of STI and abuse is indicated for translation of community-based health promotion interventions for amelioration of potential adverse sexual health outcomes among ethnic minority adolescent women.

Functional Data Analysis for Dynamical System Identification of Behavioral Processes. Trail JB, Collins LM, Rivera DE, Li R, Piper ME, Baker TB. Psychol Methods. 2013.
Efficient new technology has made it straightforward for behavioral scientists to collect anywhere from several dozen to several thousand dense, repeated measurements on one or more time-varying variables. These intensive longitudinal data (ILD) are ideal for examining complex change over time but present new challenges that illustrate the need for more advanced analytic methods. For example, in ILD the temporal spacing of observations may be irregular, and individuals may be sampled at different times. Also, it is important to assess both how the outcome changes over time and the variation between participants' time-varying processes to make inferences about a particular intervention's effectiveness within the population of interest. The methods presented in this article integrate 2 innovative ILD analytic techniques: functional data analysis and dynamical systems modeling. An empirical application is presented using data from a smoking cessation clinical trial. Study participants provided 42 daily assessments of pre-quit and post-quit withdrawal symptoms. Regression splines were used to approximate smooth functions of craving and negative affect and to estimate the variables' derivatives for each participant. The authors then modeled the dynamics of nicotine craving using standard input-output dynamical systems models. These models provide a more detailed characterization of the post-quit craving process than do traditional longitudinal models, including information regarding the type, magnitude, and speed of the response to an input. The results, in conjunction with standard engineering control theory techniques, could potentially be used by tobacco researchers to develop a more effective smoking intervention.

What Do Veterans Service Organizations' Web Sites Say About Tobacco Control? Poston WSC, Haddock CK, Jahnke SA, Jitnarin N. Am J Health Promot. 2013.
Little is known about veterans service organizations (VSOs) and their perspectives on veterans smoking or military tobacco control. Veterans have high smoking rates and many started smoking in the military, where a culture promoting use exists. A qualitative content analysis of VSO Web sites was conducted to classify health topics and identify tobacco-related information. Web sites were coded by trained raters from January to June of 2011. Data were entered, cleaned, and analyzed from July 2011 to January 2012. Twenty-four active VSO Web sites meeting inclusion criteria were rated independently. A comprehensive form was used to code 15

veteran-relevant health topics across multiple content areas/domains within the Web sites. Raters achieved 94.5% interrater agreement over nearly 5000 data points. Health content was coded as present or not within multiple VSO Web site areas/domains. The frequency of coverage by each VSO Web site and the number of VSO Web sites that mentioned a health topic in different Web site areas/domains were tabulated. A total of 277 health topics were addressed, with the top five being insurance/Tricare/Veterans Administration issues (28.2%), posttraumatic stress disorder (PTSD; 15.5%), disability/amputation/wounds (13.4%), Agent Orange (10.5%), and traumatic brain injury (9.0%). Tobacco was mentioned four times (1.4%) across all 24 VSO Web sites, and smoking cessation was never addressed. The authors conclude that VSO Web sites provide little information on tobacco-related topics and none offered information about smoking cessation. Given the high rates of tobacco use among veterans and active-duty service members, and the interaction between smoking and PTSD symptoms and treatment outcomes, VSOs should consider making tobacco control and smoking cessation higher-priority health issues on their Web sites.

Transitions in Latent Classes of Sexual Risk Behavior Among Young Injection Drug Users Following HIV Prevention Intervention. Mackesy-Amiti ME, Ouellet LJ, Finnegan L, Hagan H, Golub E, Latka M, Wagner K, Garfein RS. AIDS Behav. 2013.
The authors analyzed data from a large randomized HIV/HCV prevention intervention trial with young injection drug users (IDUs). Using categorical latent variable analysis, the authors identified distinct classes of sexual behavior for men and women. They conducted a latent transition analysis to test the effect of the intervention on transitions from higher to lower risk classes. Men who were in a high-risk class at baseline who received the intervention were 86% more likely to be in a low-risk class at follow-up compared to those in the control group ($p=0.025$). High-risk intervention participants were significantly more likely to transition to the class characterized by unprotected sex with a main partner only, while low-risk intervention participants were significantly less likely to transition to that class. No intervention effect was detected on the sexual risk behavior of women, or of men who at baseline were having unprotected sex with a main partner only.

Youths' Substance Use and Changes in Parental Knowledge-Related Behaviors During Middle School: A Person-Oriented Approach. Lippold MA, Greenberg MT, Collins LM. J Youth Adolesc. 2013.
Parental knowledge is a key protective factor for youths' risky behavior. Little is known about how longitudinal combinations of knowledge-related behaviors are associated with youths' substance use. This longitudinal study uses Latent Transition Analysis to identify latent patterns of parental knowledge-related behaviors occurring in mother-youth dyads during middle school and to investigate how changes in knowledge-related patterns are associated with youths' substance use in Grade 6 and the initiation of substance use from Grade 6 to 8. Using a sample of 536 rural dyads (53% female, 84% White), the authors assessed mother and youths' reports of parental knowledge, active parental monitoring efforts, youth disclosure, and parent-youth communication to identify six latent patterns of knowledge-related behaviors: High Monitors, Low Monitors, Communication-Focused, Supervision-Focused, Maternal Over-Estimators, and Youth Over-Estimators. Fifty percent or more of dyads in the High Monitors, Communication-Focused and Youth Over-Estimators were in the same status in both 6th and 8th grade: 98% of Low Monitors in Grade 6 were also in this status in Grade 8. The initiation of alcohol, smoking,

and marijuana was associated significantly with transitions between patterns of knowledge-related behaviors. The initiation of alcohol and smoking were associated with increased odds of transitions into the Low Monitors from the Communication-Focused, Supervision-Focused, and Maternal Over-Estimators. However, the initiation of substance use was associated with decreased odds of transitions from the High Monitors to the Low Monitors and with increased odds of transitions from High Monitors to Supervision-Focused. The discussion focuses on the value of using a person-oriented dyadic approach with multiple reporters to study changes in knowledge-related behaviors over the middle school period.

Trajectories of Mothers' Discipline Strategies and Interparental Conflict: Interrelated Change during Middle Childhood. Lansford JE, Staples AD, Bates JE, Pettit GS, Dodge KA. J Fam Commun. 2013; 13(3): 178-195.
Using data collected annually when children were in kindergarten through 3rd grade (N = 478), this study investigated changes in mothers' use of nonharsh, harsh verbal, and physical discipline; changes in interparental conflict; and associations between changes in discipline and interparental conflict. Controlling for potential confounds, physical discipline decreased over the course of middle childhood, whereas harsh verbal and nonharsh discipline remained stable. Increases in interparental conflict were associated with increases in physical discipline; decreases in interparental conflict were associated with decreases in physical discipline. Change in interparental conflict was unrelated to change in harsh verbal or nonharsh discipline, although more frequent interparental conflict was associated with more frequent use of all three types of discipline in 1st grade. Findings extend previous research on how two major forms of communication within families-conflict between parents and parents' attempts to influence their children through discipline-change across middle childhood.

Alcohol and Drug Use Among Young Adults Driving To A Drinking Location. Voas RB, Johnson MB, Miller BA. Drug Alcohol Depend. 2013; 132(1-2): 69-73.
Clubs that feature electronic music dance events (EMDEs) draw young adults aged 18-34 who are at high-risk for alcohol-related crashes to locations where alcohol sales are the principal source of revenue. Up to 30% of these attendees may also use drugs. This provides an important context in which to study driving arrangements that reflect concern with impaired driving. The authors explored whether drivers were using less alcohol and fewer drugs at exit than their passengers were and whether a driver for the group ever changed after consuming too much during the evening. Using biological measures of alcohol consumption (breath tests) and drug use (oral fluid tests), 175 drivers and 272 passengers were surveyed among young adults arriving at and departing from EMDEs in San Francisco. Upon exit from the drinking locations, only 20% of the drivers, compared to 47% of the passengers, had a high breath alcohol concentration (defined as a BrAC of .05g/dL or greater). Further, there was evidence that drivers with high BrACs switched to passenger status on exit and former passengers with lower BrACs replaced those drivers. However, there were no differences in the prevalence of drug use among drivers and passengers. These findings suggest that the effort by young adult drivers to avoid alcohol-impaired driving appears to be reducing the number of drivers with high BrACs returning from drinking locations, such as EMDEs, by about one third. However, there is no similar pattern for drugged driving.

Adolescents In Wartime US Military Families: A Developmental Perspective On Challenges and Resources. Milburn NG, Lightfoot M. Clin Child Fam Psychol Rev. 2013; 16(3): 266-277.
Adolescents in wartime US military families are a unique group of young people who are experiencing the usual milestones of adolescent development, including establishing their identities and becoming autonomous, while they face the challenges of military life such as multiple frequent moves, relocation, and parent deployment to combat settings. This paper reviews research on adolescents in wartime US military families, within the context of adolescent development, to identify their behavioral, emotional and academic risk status, and challenges and resources. Recommendations for future research and interventions to foster the healthy development of these adolescents are also provided.

Family Risk As A Predictor Of Initial Engagement and Follow-Through In A Universal Nurse Home Visiting Program To Prevent Child Maltreatment. Alonso-Marsden S, Dodge KA, O'Donnell KJ, Murphy RA, Sato JM, Christopoulos C. Child Abuse Negl. 2013; 37(8): 555-565.
As nurse home visiting to prevent child maltreatment grows in popularity with both program administrators and legislators, it is important to understand engagement in such programs in order to improve their community-wide effects. This report examines family demographic and infant health risk factors that predict engagement and follow-through in a universal home-based maltreatment prevention program for new mothers in Durham County, North Carolina. Trained staff members attempted to schedule home visits for all new mothers during the birthing hospital stay, and then nurses completed scheduled visits three to five weeks later. Medical record data was used to identify family demographic and infant health risk factors for maltreatment. These variables were used to predict program engagement (scheduling a visit) and follow-through (completing a scheduled visit). Program staff members were successful in scheduling 78% of eligible families for a visit and completing 85% of scheduled visits. Overall, 66% of eligible families completed at least one visit. Structural equation modeling (SEM) analyses indicated that high demographic risk and low infant health risk were predictive of scheduling a visit. Both low demographic and infant health risk were predictive of visit completion. Findings suggest that while higher demographic risk increases families' initial engagement, it might also inhibit their follow-through. Additionally, parents of medically at-risk infants may be particularly difficult to engage in universal home visiting interventions. Implications for recruitment strategies of home visiting programs are discussed.

A Dynamical Systems Approach to Understand Self-Regulation in Smoking Cessation Behavior Change. Timms KP, Rivera DE, Collins LM, Piper ME. Nicotine Tob Res. 2013.
Self-regulation, a key component of the addiction process, has been challenging to model precisely in smoking cessation settings, largely due to the limitations of traditional methodological approaches in measuring behavior over time. However, increased availability of intensive longitudinal data (ILD) measured through ecological momentary assessment facilitates the novel use of an engineering modeling approach to better understand self-regulation. Dynamical systems modeling is a mature engineering methodology that can represent smoking cessation as a self-regulation process. This article shows how a dynamical systems approach effectively captures the reciprocal relationship between day-to-day changes in craving and smoking. Models are estimated using ILD from a smoking cessation randomized clinical trial.A

system of low-order differential equations is presented that models cessation as a self-regulatory process. It explains 87.32% and 89.16% of the variance observed in craving and smoking levels, respectively, for an active treatment group and 62.25% and 84.12% of the variance in a control group. The models quantify the initial increase and subsequent gradual decrease in craving occurring postquit as well as the dramatic quit-induced smoking reduction and postquit smoking resumption observed in both groups. Comparing the estimated parameters for the group models suggests that active treatment facilitates craving reduction and slows postquit smoking resumption. This article illustrates that dynamical systems modeling can effectively leverage ILD in order to understand self-regulation within smoking cessation. Such models quantify group-level dynamic responses in smoking cessation and can inform the development of more effective interventions in the future.

The Timing of School Transitions and Early Adolescent Problem Behavior. Lippold MA, Powers CJ, Syvertsen AK, Feinberg ME, Greenberg MT J Early Adolesc. 2013 Aug 1; 33(6): 821-844.
This longitudinal study investigates whether rural adolescents who transition to a new school in sixth grade have higher levels of risky behavior than adolescents who transition in seventh grade. The authors' findings indicate that later school transitions had little effect on problem behavior between sixth and ninth grades. Cross-sectional analyses found a small number of temporary effects of transition timing on problem behavior: Spending an additional year in elementary school was associated with higher levels of deviant behavior in the Fall of Grade 6 and higher levels of antisocial peer associations in Grade 8. However, transition effects were not consistent across waves and latent growth curve models found no effects of transition timing on the trajectory of problem behavior. The authors discuss policy implications and compare our findings with other research on transition timing.

The Mental Health, Substance Use, and Delinquency among Truant Youths in a Brief Intervention Project: A Longitudinal Study. Dembo R, Briones-Robinson R, Barrett K, Winters KC, Schmeidler J, Ungaro R, Karas LM, Belenko S, Gulledge L. J Emot Behav Disord. 2013; 21 (3):176-192.
The relationship between substance use, mental health disorders, and delinquency among youth is well documented. What has received far less attention from researchers is the relationship between these issues among truant youth, in spite of studies that document truants are a population at-risk for negative outcomes. The present study bridges this gap by (1) examining psychosocial functioning and delinquency among truants, and (2) assessing the efficacy of a Brief Intervention (BI) in reducing delinquent behavior over time. To meet these objectives, data were collected from 183 truant youth enrolled in an ongoing NIDA-funded BI project. Informed by a developmental damage perspective, a structural equation model was formulated and estimated. Interim results provide overall support for the model, and suggest the BI may be a promising, innovative intervention for truant youth. Service delivery implications and directions for future analyses are discussed.

Changes In Friends' and Parental Influences On Cigarette Smoking From Early Through Late Adolescence. Liao Y, Huang Z, Huh J, Pentz MA, Chou C-P. J Adolesc Health. 2013; 53(1): 132-138.
This study examined the changes in friends' and parental influences on cigarette smoking across two developmentally distinct social environments for adolescents: junior high school and high school. Longitudinal data consisting of seven repeated measures following 1,001 adolescents from 7th to 12th grade was obtained from the Midwestern Prevention Project. A two-piece Growth Curve Model (GCM) was used to assess the growth trajectory of current cigarette use: one piece for the junior high school period, and the other for the high school period. Perceived friends' and parental cigarette use were each used as a time-varying covariate in separate GCMs. Effects of friends' and parental cigarette use remained significant on adolescent cigarette smoking across the two developmental periods. The magnitude of friends' effect was in general higher during junior high school than high school. The magnitude of the parental effect remained relatively stable between the two periods. However, decreasing trends in both effects were observed from 10th to 12th grade. Gender differences also emerged. Friends' and parental effects were greater for girls in their early high school years, whereas friends' effect decreased in magnitude among girls and increased among boys during high school. The transition from junior high school to high school represents an opportunity for interventions to counteract peer influence given that such influence appeared to be much weaker during this period. However, interventions should continue to target parents as their behavior remains influential through the end of high school.

Transitional Life Events and Trajectories Of Cigarette and Alcohol Use During Emerging Adulthood: Latent Class Analysis and Growth Mixture Modeling. Huh J, Huang Z, Liao Y, Pentz MA, Chou C-P. J Stud Alcohol Drugs. 2013; 74(5): 727-735.
Emerging adulthood (ages 18-25 years) has been associated with elevated substance use. Transitional life events (TLEs) during emerging adulthood in relation to substance use are usually examined separately, rather than as a constellation. The purposes of this study were (a) to explore distinct subgroups experiencing various TLEs during emerging adulthood, (b) to identify heterogeneous trajectories of cigarette and alcohol use during emerging adulthood, and (c) to examine the association of TLEs with cigarette and alcohol use trajectories. Five waves of longitudinal data (mean age range: 19.5-26.0 years) were used from a community-based drug prevention program (n = 946, 49.9% female). Distinct subgroups of emerging adults who experienced various TLEs were identified using latent class analysis. Cigarette and alcohol use were examined using a latent growth mixture model. A three-class model fit the data best in identifying TLE subgroups (new family, college attenders [NFCA]; uncommitted relationships, college attenders [URCA]; hibernators [HBN]). Three-trajectory models fit the data best for cigarette and alcohol use during emerging adulthood. The TLE categories were significantly associated with the cigarette ($p < .05$) and alcohol use groups ($p < .001$); specifically, the URCA and HBN groups were significantly more likely to be classified as accelerating cigarette users, relative to NFCA ($ps < .05$). The NFCA and HBN groups were significantly more likely to be classified as accelerating alcohol users, relative to URCA ($ps < .01$). To characterize an "at-risk" emerging adult group for cigarette and alcohol use over time, a range of life events during emerging adulthood should be considered. Interventions tailored to young adulthood may benefit from targeting the absence of these life events typifying "independence" as a potential marker for

underlying substance use problems and provide supplemental screening methods to identify young adults with similar issues.

Gender Differences in the Use of Drug Resistance Strategies: An Analysis of Rural Asian/Pacific Islander Youth. Okamoto SK, Pel S, Helm S, Valdez JK. Health Promot Pract. 2013.
This study examines gender differences in the use of drug resistance strategies for rural Asian/Pacific Islander youth. Multiethnic Asian/Pacific Islander youth (N = 213) from six middle/intermediate schools on the Island of Hawai'i participated in the study, and gender differences in their real-world use of specific strategies (e.g., refuse, explain, avoid, leave) were examined. Despite similar levels of exposure to situations where drugs and/or alcohol were offered, girls indicated significantly lower usage of most of the resistance strategies compared to boys, suggesting girls' increased risk in dealing with drug-related problem situations. Implications for gender-and culture-specific health promotion and drug prevention curricula are discussed.

Late-Life Depressive Symptoms: Prediction Models Of Change. Garcia-Pena C, Wagner FA, Sanchez-Garcia S, Espinel-Bermudez C, Juarez-Cedillo T, Perez-Zepeda M, Arango-Lopera V, Franco-Marina F, Ramirez-Aldana R, Gallo JJ. J Affect Disord. 2013; 150(3): 886-894.
Depression is a well-recognised problem in the elderly. The aim of this study was to determine the factors associated with predictors of change in depressive symptoms, both in subjects with and without baseline significant depressive symptoms. Longitudinal study of community-dwelling elderly people (>60 years or older), baseline evaluations, and two additional evaluations were reported. Depressive symptoms were measured using a 30-item geriatric depression scale, and a score of 11 was used as cut-off point for significant depressive symptoms in order to stratify the analyses in two groups: with significant depressive symptoms and without significant depressive symptoms. Sociodemographic data, social support, anxiety, cognition, positive affect, control locus, activities of daily living, recent traumatic life events, physical activity, comorbidities, and quality of life were evaluated. Multi-level generalised estimating equation model was used to assess the impact on the trajectory of depressive symptoms. A number of 7882 subjects were assessed, with 29.42% attrition. At baseline assessment, mean age was 70.96 years, 61.15% were women. Trajectories of depressive symptoms had a decreasing trend. Stronger associations in those with significant depressive symptoms, were social support (OR.971, p<.001), chronic pain (OR 2.277, p<.001) and higher locus of control (OR.581, p<.001). In contrast for those without baseline significant depressive symptoms anxiety and a higher locus of control were the strongest associations. New insights into late-life depression are provided, with special emphasis in differentiated factors influencing the trajectory when stratifying regarding basal status of significant depressive symptoms. The study has not included clinical evaluations and nutritional assessments.

A Randomized Controlled Trial Of A Group Motivational Interviewing Intervention For Adolescents With A First Time Alcohol Or Drug Offense. D'Amico EJ, Hunter SB, Miles JNV, Ewing BA, Osilla KC. J Subst Abuse Treat. 2013; 45(5): 400-408.
Group motivational interviewing (MI) interventions that target youth at-risk for alcohol and other drug (AOD) use may prevent future negative consequences. Youth in a teen court setting [n=193; 67% male, 45% Hispanic; mean age 16.6 (SD=1.05)] were randomized to receive either

a group MI intervention, Free Talk, or usual care (UC). The authors examined client acceptance, and intervention feasibility and conducted a preliminary outcome evaluation. Free Talk teens reported higher quality and satisfaction ratings, and MI integrity scores were higher for Free Talk groups. AOD use and delinquency decreased for both groups at 3 months, and 12-month recidivism rates were lower but not significantly different for the Free Talk group compared to UC. Results contribute to emerging literature on MI in a group setting. A longer term follow-up is warranted.

Internalizing Antecedents and Consequences of Binge-Eating Behaviors in a Community-Based, Urban Sample of African American Females. Musci RJ, Hart SR, Ialongo N. Prev Sci. 2013.
The etiology of problem-eating behaviors is often overlooked in research as it typically shares many symptoms with other more common psychiatric illnesses. Binge-eating problems are at the forefront of the popular media because of the connection to obesity; therefore, increased knowledge of binge eating problems, particularly the internalizing antecedents and consequences will have implications in a multitude of domains, including prevention programs aimed at physical and mental health. The current study examines the antecedents of binge-eating behaviors by exploring how the growth of internalizing symptoms influences the proximal outcome of a binge-eating inventory in a longitudinal sample of African American girls. Additional consequences of binge-eating problems are also explored. This study focuses on binge-eating problems in order to present valuable information for prevention scientists who wish to develop target individuals at high risk for internalizing problems such as suicide.

Deconstructing the Externalizing Spectrum: Growth Patterns Of Overt Aggression, Covert Aggression, Oppositional Behavior, Impulsivity/Inattention, and Emotion Dysregulation Between School Entry and Early Adolescence. Olson SL, Sameroff AJ, Lansford JE, Sexton H, Davis-Kean P, Bates JE, Pettit GS, Dodge KA. Dev Psychopathol. 2013; 25(3): 817-842.
The purpose of this study was to determine whether five subcomponents of children's externalizing behavior showed distinctive patterns of long-term growth and predictive correlates. The authors examined growth in teachers' ratings of overt aggression, covert aggression, oppositional defiance, impulsivity/inattention, and emotion dysregulation across three developmental periods spanning kindergarten through Grade 8 (ages 5-13 years). They also determined whether three salient background characteristics, family socioeconomic status, child ethnicity, and child gender, differentially predicted growth in discrete categories of child externalizing symptoms across development. Participants were 543 kindergarten-age children (52% male, 81% European American, 17% African American) whose problem behaviors were rated by teachers each successive year of development through Grade 8. Latent growth curve analyses were performed for each component scale, contrasting with overall externalizing, in a piecewise fashion encompassing three developmental periods: kindergarten-Grade 2, Grades 3-5, and Grades 6-8. The authors found that most subconstructs of externalizing behavior increased significantly across the early school age period relative to middle childhood and early adolescence. However, overt aggression did not show early positive growth, and emotion dysregulation significantly increased across middle childhood. Advantages of using subscales were most clear in relation to illustrating different growth functions between the discrete developmental periods. Moreover, growth in some discrete subcomponents was differentially associated with variations in family socioeconomic status and ethnicity. These findings strongly

affirmed the necessity of adopting a developmental approach to the analysis of growth in children's externalizing behavior and provided unique data concerning similarities and differences in growth between subconstructs of child and adolescent externalizing behavior.

A Community's Response To Suicide Through Public Art: Stakeholder Perspectives From the Finding the Light Within Project. Mohatt NV, Singer JB, Evans Jr, AC, Matlin SL, Golden J, Harris C, Burns J, Siciliano C, Kiernan G, Pelleritti M, Tebes JK. Am J Community Psychol. 2013; 52(1-2): 197-209.
Suicide is a preventable public health problem and a leading cause of death in the United States. Despite recognized need for community-based strategies for suicide prevention, most suicide prevention programs focus on individual-level change. This article presents seven first person accounts of Finding the Light Within, a community mobilization initiative to reduce the stigma associated with suicide through public arts participation that took place in Philadelphia, Pennsylvania from 2011 through 2012. The stigma associated with suicide is a major challenge to suicide prevention, erecting social barriers to effective prevention and treatment and enhancing risk factors for people struggling with suicidal ideation and recovery after losing a loved one to suicide. This project engaged a large and diverse audience and built a new community around suicide prevention through participatory public art, including community design and production of a large public mural about suicide, storytelling and art workshops, and a storytelling website. The authors present this project as a model for how arts participation can address suicide on multiple fronts-from raising awareness and reducing stigma, to promoting community recovery, to providing healing for people and communities in need.

Alcohol Consumption, Heavy Drinking, and Mortality: Rethinking the J-Shaped Curve. Plunk AD, Syed-Mohammed H, Cavazos-Rehg P, Bierut LJ, Grucza RA. Alcohol Clin Exp Res. 2013.
High average daily consumption of alcohol has been associated with elevated mortality risk, but more moderate consumption, relative to abstinence, has been associated with reduced mortality risk. However, average daily consumption can be complicated to assess, limiting its usefulness in both research and clinical practice. There are also concerns that average consumption fails to capture the risk associated with certain drinking patterns, such as heavy episodic drinking. This study assessed mortality associated with drinking pattern, operationalized as the frequency of both heavy and nonheavy drinking occasions. Data from the 1997 to 2001 administrations of the National Health Interview Survey (NHIS; n=111,511) were paired with the current release of the NHIS Linked Mortality Files, which provided mortality follow-up data through the end of 2006. The authors estimated the impact of drinking pattern on all-cause mortality, operationalized as the frequency of heavy (5+ drinks) and nonheavy (<5 drinks) drinking occasions. Other covariates in the model included survey wave, sex, age, race/ethnicity, ratio of family income to poverty threshold, educational attainment, body mass index, and smoking status. Over a third of past-year drinkers reported heavy drinking. Mortality risk increased steadily as heavy drinking frequency increased; daily heavy drinkers exhibited an almost 2-fold risk of death compared with abstainers ($p<0.001$). Regular nonheavy drinking was associated with decreased mortality, similar to the "J-shaped curve" highlighted in past research on alcohol mortality; this potential protective effect peaked around 2 nonheavy occasions per week. Any heavy drinking likely elevates mortality risk, and substantial health benefits could be realized by reducing heavy drinking occasions or limiting overall drinking. Heavy and nonheavy drinking frequencies are

valid targets for clinical screening and could be helpful in assessing risk and promoting less harmful drinking behavior.

Time-Varying Effect Moderation Using the Structural Nested Mean Model: Estimation Using Inverse-Weighted Regression With Residuals. Almirall D, Griffin BA, McCaffrey DF, Ramchand R, Yuen RA, Murphy SA. Stat Med. 2013.
This article considers the problem of examining time-varying causal effect moderation using observational, longitudinal data in which treatment, candidate moderators, and possible confounders are time varying. The structural nested mean model (SNMM) is used to specify the moderated time-varying causal effects of interest in a conditional mean model for a continuous response given time-varying treatments and moderators. The authors present an easy-to-use estimator of the SNMM that combines an existing regression-with-residuals (RR) approach with an inverse-probability-of-treatment weighting (IPTW) strategy. The RR approach has been shown to identify the moderated time-varying causal effects if the time-varying moderators are also the sole time-varying confounders. The proposed IPTW+RR approach provides estimators of the moderated time-varying causal effects in the SNMM in the presence of an additional, auxiliary set of known and measured time-varying confounders. The authors use a small simulation experiment to compare IPTW+RR versus the traditional regression approach and to compare small and large sample properties of asymptotic versus bootstrap estimators of the standard errors for the IPTW+RR approach. This article clarifies the distinction between time-varying moderators and time-varying confounders. The authors illustrate the methodology in a case study to assess if time-varying substance use moderates treatment effects on future substance use.

HIV Among Injection Drug Users and Their Intimate Partners In Almaty, Kazakhstan. El-Bassel N, Gilbert L, Terlikbayeva A, Wu E, Beyrer C, Shaw S, Hunt T, Ma X, Chang M, Ismayilova L, Tukeyev M, Zhussupov B, Rozental Y. AIDS Behav. 2013; 17(7): 2490-2500.
This paper examines prevalence rates of HIV, HCV, and syphilis among a sample of injecting drug users (IDUs) and their heterosexual intimate partners (N=728) from Almaty, Kazakhstan. The study uses baseline data from Project Renaissance, a couple-based HIV prevention intervention delivered to a couple where one or both partners are IDUs. HIV prevalence rates among female and male IDUs were 28%. Among the full sample, 75% had HCV, and 13% tested positive for the syphilis antibody test. Only 10% of the sample ever visited a needle exchange program. One-fourth (25.3%) had never been tested for HIV. One-quarter of those who tested positive were unaware of their status. Being HIV positive was associated with a history of incarceration, being an IDU, and having access to needle exchange programs. The findings call for increasing efforts to improve access to HIV testing, prevention, treatment, and care for IDUs in Almaty, Kazakhstan.

Trauma, Delinquency, and Substance Use: Co-occurring Problems for Adolescent Girls in the Juvenile Justice System. Smith DK, Saldana L. J Child Adolesc Subst Abuse. 2013; 22(5): 450-465.
Girls in the juvenile justice system are known to have high rates of co-occurring childhood abuse, trauma, and substance abuse. Girls with this constellation of problems are at high risk for serious adverse outcomes, including problems with drug dependence and abuse. The relationship between childhood sexual abuse, childhood physical abuse, other types of childhood trauma, and

rates of substance use during adolescence were examined for girls in the juvenile justice system. As expected, childhood sexual abuse was significantly related to girls' substance use during adolescence. In contrast to prior research, no link was found between physical abuse, lifetime trauma, and substance use. Limitations and future directions are discussed.

Pharmacokinetic and Pharmacodynamic Profile Of Supratherapeutic Oral Doses Of Δ(9) -THC In Cannabis Users. Lile JA, Kelly TH, Charnigo RJ, Stinchcomb AL, Hays LR. J Clin Pharmacol. 2013; 53(7): 680-690.
Oral (9) -tetrahydrocannabinol ((9) -THC) has been evaluated as a medication for cannabis dependence, but repeated administration of acute oral doses up to 40mg has not been effective at reducing drug-taking behavior. Larger doses might be necessary to affect cannabis use. The purpose of the present study was therefore to determine the physiological and behavioural effects of oral (9) -THC at acute doses higher than those tested previously. The pharmacokinetic and pharmacodynamic profile of oral (9) -THC, administered in ascending order in 15mg increments across separate sessions, up to a maximum of 90mg, was determined in seven cannabis users. Five subjects received all doses and two experienced untoward side effects at lower doses. (9) -THC produced a constellation of effects consistent with previous clinical studies. Low cannabinoid concentrations were associated with significant effects on drug-sensitive measures, although progressively greater levels did not lead to proportionately larger drug effects. Considerable variability in Cmax and tmax was observed. Doses of oral (9) -THC larger than those tested previously can be administered to individuals with a history of cannabis use, although given the pharmacokinetic variability of oral (9) -THC and individual differences in sensitivity, individualized dose adjustment is needed to avoid side effects and maximize therapeutic response.

Mobile Health Technology Evaluation: The Mhealth Evidence Workshop. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, Riley WT, Shar A, Spring B, Spruijt-Metz D, Hedeker D, Honavar V, Kravitz R, Lefebvre RC, Mohr DC, Murphy SA, Quinn C, Shusterman V, Swendeman D. Am J Prev Med. 2013; 45(2): 228-236.
Creative use of new mobile and wearable health information and sensing technologies (mHealth) has the potential to reduce the cost of health care and improve well-being in numerous ways. These applications are being developed in a variety of domains, but rigorous research is needed to examine the potential, as well as the challenges, of utilizing mobile technologies to improve health outcomes. Currently, evidence is sparse for the efficacy of mHealth. Although these technologies may be appealing and seemingly innocuous, research is needed to assess when, where, and for whom mHealth devices, apps, and systems are efficacious. In order to outline an approach to evidence generation in the field of mHealth that would ensure research is conducted on a rigorous empirical and theoretic foundation, on August 16, 2011, researchers gathered for the mHealth Evidence Workshop at NIH. The current paper presents the results of the workshop. Although the discussions at the meeting were cross-cutting, the areas covered can be categorized broadly into three areas: (1) evaluating assessments; (2) evaluating interventions; and (3) reshaping evidence generation using mHealth. This paper brings these concepts together to describe current evaluation standards, discuss future possibilities, and set a grand goal for the emerging field of mHealth research.

The Role Of the Self-Fulfilling Prophecy In Young Adolescents' Responsiveness To A Substance Use Prevention Program. Madon S, Scherr KC, Spoth R, Guyll M, Willard J, Vogel DL. J Appl Soc Psychol. 2013; 43(9): 1784-1798.
This research examined whether naturally-occurring self-fulfilling prophecies influenced adolescents' responsiveness to a substance use prevention program. The authors addressed this issue with a unique methodological approach that was designed to enhance the internal validity of research on naturally-occurring self-fulfilling prophecies by experimentally controlling for prediction without influence. Participants were 321 families who were assigned to an adolescent substance use prevention program that either did or did not systematically involve parents. Results showed that parents' perceptions about the value of involving parents in adolescent substance use prevention predicted adolescents' alcohol use more strongly among families assigned to the prevention program that systematically involved parents than to the one that did not. The theoretical and practical implications of these findings are discussed.

Perceived Norms Moderate the Association Between Mental Health Symptoms and Drinking Outcomes Among At-Risk Adolescents. Pedersen ER, Miles JNV, Hunter SB, Osilla KC, Ewing BA, D'Amico EJ. J Stud Alcohol Drugs. 2013; 74(5): 736-745.
There has been limited research examining the association between mental health symptoms, perceived peer alcohol norms, and alcohol use and consequences among samples of adolescents. The current study used a sample of 193 at-risk youths with a first-time alcohol and/or other drug offense in the California Teen Court system to explore the moderating role of perceived peer alcohol norms on the association between mental health symptoms and drinking outcomes. Measures of drinking, consequences, mental health symptoms, and perceived peer alcohol norms were taken at baseline, with measures of drinking and consequences assessed again 6 months later. Regression analyses examined the association of perceived norms and mental health symptoms with concurrent and future drinking and consequences. The authors found that higher perceived drinking peer norms were associated with heavy drinking behavior at baseline and with negative alcohol consequences both at baseline and 6 months later. Also, perceived drinking norms moderated the association between mental health symptoms and alcohol-related consequences such that better mental health was related to increased risk for alcohol-related consequences both concurrently and 6 months later among those with higher baseline perceptions of peer drinking norms. Findings demonstrate the value of norms-based interventions, especially among adolescents with few mental health problems who are at risk for heavy drinking.

Gestational Weight Gain Of Pregnant African American Adolescents Affects Body Mass Index 18 Years Later. Groth SW, Holland ML, Kitzman H, Meng Y. J Obstet Gynecol Neonatal Nurs. 2013; 42(5): 541-550.
The aim of this study was to determine if gestational weight gain (GWG) in adolescents is associated with long-term weight increases 12years and 18years after delivery of a first child and the differential effects of weight gain during pregnancy that is inadequate, the appropriate amount, and excessive based on the 2009 Institute of Medicine (IOM) recommendations. This was a secondary analysis of data from a randomized controlled trial conducted in Memphis, Tennessee. Two hundred ninety-eight (298) primiparous low-income Black women who were adolescents at the time of their first pregnancies served as subjects. Linear regression was used to examine the relationship between body mass index (BMI) at 12 and 18years postdelivery and

GWG, parity, prepregnancy BMI, and smoking. The total sample experienced a significant BMI increase from prepregnancy to 12-years and 18-years postdelivery. More than 50% of the women had a BMI increase greater than 10kg/m(2). By 18-years postdelivery, 85% were overweight or obese. Prepregnancy BMI and GWG had a positive significant effect on BMI 12 and 18-years later, whereas smoking had a negative effect. Those who gained excessive weight based on the IOM recommendations had a significantly higher BMI compared with those who gained appropriately. Gestational weight gain had long-term effects on BMI in a minority adolescent population. Excessive pregnancy weight gain is likely to contribute to long-term weight retention, especially if adolescents are overweight or obese when they become pregnant with their first children. Intervention during pregnancy to limit GWG has the potential of limiting long-term negative health consequences that result from overweight and obesity in minority women.

Attention Problems and Academic Achievement: Do Persistent and Earlier-Emerging Problems Have More Adverse Long-Term Effects? Rabiner DL, Carrig MM, Dodge KA. J Atten Disord. 2013.

This study examined whether the negative association between children's attention difficulties and their academic functioning is largely confined to children whose attention problems persist across early grades and whether it depends on when attention problems emerge in children's schooling. Children from the normative sample of the Fast Track study were classified into four attention problem groups based on the presence versus absence of attention problems in first and second grade. Those with attention problems in both grades showed a decline in reading and math achievement during the K-5 interval relative to children with attention problems in first grade only. Both groups of inattentive first graders also performed worse than comparison children. In contrast, children whose attention problems emerged in second grade did not differ from comparison children on any achievement outcome performed significantly better than inattentive first graders. The implications of these findings are discussed.

Predictors Of Health Behaviors After the Economic Downturn: A Longitudinal Study. Macy JT, Chassin L, Presson CC. Soc Sci Med. 2013; 89: 8-15.

Economic declines and their associated stress, shortage of financial resources, and changes in available time can impair health behaviors. This study tested the association between change in working hours, change in employment status, and financial strain and health behaviors measured after the 2008 recession after controlling for pre-recession levels of the health behaviors. The moderating influences of demographic factors and pre-recession levels of the health behaviors on the association between change in working hours and employment status and financial strain and the health behaviors were also tested. Participants (N = 3984) were from a longitudinal study of a U.S. Midwestern community-based sample. Regression analyses tested the unique relations between change in hours worked per week, change in employment status, and financial strain and five health behaviors over and above demographic factors and pre-recession levels of the same behavior. Models included predictor by covariate interactions. Participants who reported higher levels of financial strain engaged in lower levels of all but one of the five health behaviors, but there were no significant main effects of a change in the number of hours worked per week or change in employment status. Significant interactions revealed moderation of these relations by demographic characteristics, but findings differed across health behaviors. Financial strain negatively affected engagement in multiple healthy behaviors. Promoting the maintenance

of healthy behaviors for disease prevention is an important public health goal during times of economic decline.

Developmental Trajectories Of Maladaptive Perfectionism Among African American Adolescents. Herman KC, Wang K, Trotter R, Reinke WM, Ialong N. Child Dev. 2013; 84(5): 1633-1650.
This study examined the developmental trajectories of maladaptive perfectionism over a 7-year period among African American youth living in an urban setting (N=547). In particular, the study attempted to determine whether two maladaptive aspects of perfectionism (socially prescribed and self-critical) changed over time and could be distinguished by variables in 6th and 12th grades (Mage at study entry [first grade] was 6.22 years [SD=0.34]). Four classes best described the developmental trajectories on both measures of maladaptive perfectionism: high, low, increasing, and decreasing. Sixth- and 12th-grade correlates, including measures of internalizing symptoms, mostly confirmed the distinctiveness of these classes. Parallel process analyses suggested that the two processes are complementary, yet distinct. Implications regarding the prevention of maladaptive perfectionism are discussed.

Testing Two Process Models Of Religiosity and Sexual Behavior. Vasilenko SA, Duntzee CI, Zheng Y, Lefkowitz ES. J Adolesc. 2013; 36(4): 667-673.
Adolescents who are more religious are less likely to have sex, but the process by which religiosity impacts sexual behavior is not well established. The authors tested two potential processes, involving: (1) whether religiosity suppressed individuals' motivations to have sex for physical pleasure, and (2) whether individuals internalized their religions' teachings about sex for pleasure. College students (N=610, 53.8% female, M age=18.5, 26.1% Hispanic Latino [HL], 14.9% non-HL African American, 23.8% non-HL Asian American/Pacific Islander, 26.3% non-HL European American and 8.9% non-HL multiracial) completed web surveys during their first three semesters. Religiosity did not moderate the association between students' motivations for sex for pleasure and sexual behavior. Motivations mediated the association between religiosity and sexual behavior, suggesting that religion does not override adolescents' existing motivations, but instead, religious adolescents internalize norms about sexual behavior.

The Organizational Health of Urban Elementary Schools: School Health and Teacher Functioning. Mehta TG, Atkins MS, Frazier SL. School Ment Health. 2013; 5(3): 144-154.
This study examined the factor structure of the Organizational Health Inventory-Elementary version (OHI-E; Hoy, Tarter, & Kottkamp, 1991) in a sample of 203 teachers working in 19 high-poverty, urban schools and the association of organizational school health with teacher efficacy, teacher stress, and job satisfaction. Results indicated a similar factor structure of the OHI-E as compared with the population of schools in the original sample (Hoy et al., 1991), and that specific components of organizational health, such as a positive learning environment, are associated with teacher efficacy, stress, and satisfaction. Overall, teachers' relations with their peers, their school leadership, and their students appear especially critical in high-poverty, urban schools. Recommendations for research and practice related to improving high-poverty, urban schools are presented.

An Electrophysiological Index Of Changes In Risk Decision-Making Strategies. Zhang D, Gu R, Wu T, Broster LS, Luo Yi, Jiang Y, Luo Y-J. Neuropsychologia. 2013; 51(8): 1397-1407. Human decision-making is significantly modulated by previously experienced outcomes. Using event-related potentials (ERPs), the authors examined whether ERP components evoked by outcome feedbacks could serve as biomarkers to signal the influence of current outcome evaluation on subsequent decision-making. In this study, 18 adult volunteers participated in a simple monetary gambling task, in which they were asked to choose between two options that differed in risk. Their decisions were immediately followed by outcome presentation. Temporospatial principle component analysis (PCA) was applied to the outcome-onset locked ERPs in the 200-1000 ms time window. The PCA factors that approximated classical ERP components (P2, feedback-related negativity, P3a, and P3b) in terms of time course and scalp distribution were tested for their association with subsequent decision-making strategies. These results revealed that a fronto-central PCA factor approximating the classical P3a was related to changes of decision-making strategies on subsequent trials. The decision to switch between high- and low-risk options resulted in a larger P3a relative to the decision to retain the same choice. According to the results, the authors suggest that the amplitude of the fronto-central P3a is an electrophysiological index of the influence of current outcome on subsequent risk decision-making. Furthermore, the ERP source analysis indicated that the activations of the frontopolar cortex and sensorimotor cortex were involved in subsequent changes of strategies, which enriches our understanding of the neural mechanisms of adjusting decision-making strategies based on previous experience.

Contemporary Research On Parenting: Conceptual, Methodological, and Translational Issues. Power TG, Sleddens EFC, Berge J, Connell L, Govig B, Hennessy E, Liggett L, Mallan K, Santa Maria D, Odoms-Young A, St George SM. Child Obes. 2013; 9 Suppl: S87-94. Researchers over the last decade have documented the association between general parenting style and numerous factors related to childhood obesity (e.g., children's eating behaviors, physical activity, and weight status). Many recent childhood obesity prevention programs are family focused and designed to modify parenting behaviors thought to contribute to childhood obesity risk. This article presents a brief consideration of conceptual, methodological, and translational issues that can inform future research on the role of parenting in childhood obesity. They include: (1) General versus domain specific parenting styles and practices; (2) the role of ethnicity and culture; (3) assessing bidirectional influences; (4) broadening assessments beyond the immediate family; (5) novel approaches to parenting measurement; and (6) designing effective interventions. Numerous directions for future research are offered.

Serving Homeless Veterans In the VA Desert Pacific Healthcare Network: A Needs Assessment To Inform Quality Improvement Endeavors. Gabrielian S, Yuan A, Rubenstein L, Andersen RM, Gelberg L. J Health Care Poor Underserved. 2013; 24(3): 1344-1352. This report describes a needs assessment of VA programs for homeless Veterans in Southern California and Nevada, the geographic region with the most homeless Veterans in the nation. The assessment was formulated through key informant interviews. Current service provisions are discussed, along with salient unmet needs for this vulnerable population.

Spirituality In Addictions Treatment: Wisdom To Know What It Is. Sussman S, Milam J, Arpawong TE, Tsai J, Black DS, Wills TA. Subst Use Misuse. 2013; 48(12): 1203-1217.
Spirituality has long been integrated into treatments for addiction. However, how spirituality differs from other related constructs and implications for recovery among nonspiritual persons remains a source of discussion. This article examines ways in which spirituality is delineated, identifies variables that might mediate the relations between spirituality and recovery from substance abuse disorders, describes distinctions between spiritual and nonspiritual facets of addictions treatment, and suggests means to assist in further clarification of this construct.

Immediate and Six-Month Effects Of Project EX Russia: A Smoking Cessation Intervention Pilot Program. Idrisov B, Sun P, Akhmadeeva L, Arpawong TE, Kukhareva P, Sussman S. Addict Behav. 2013; 38(8): 2402-2408.
This study evaluates the performance of the Project EX tobacco use cessation program in Russian summer recreational camps. An eight-session clinic-based tobacco use cessation program for adolescents was tested during the summer of 2011 in an experimental pilot trial that involved different youth that rotated through camps. Conditions were nested within camps. Two rotations of unique subject groups of smokers (program and standard care control) through each of five camps provided the means of controlling for campsite by condition. Assignment of condition by rotation was random (by a flip of a coin), achieving reasonable baseline comparability (total n=164 smokers at baseline, 76 program group, 88 standard care control group). Evaluation involved an immediate pretest and posttest and a six-month telephone follow-up. At immediate posttest, Project EX was moderately well-received, significantly reduced future smoking expectation (46% reduction in EX program condition versus 8% in control, $p<.0001$), decreased intention to not quit smoking (-5.2% in EX versus +1.4% in control, $p<.05$), and increased motivation to quit smoking (0.72 versus -0.04, $p<.0001$). At the six-month follow-up, program subjects reported a higher intent-to-treat quit rate during the last 30days (7.5% versus 0.1%, $p<.05$). For the subjects who remained monthly smokers at the six-month follow-up, Project EX reduced subjects' level of nicotine dependence (-0.53 versus +0.15, $p<.001$). The results were quite promising for this program, which included motivation enhancement, coping skill, and alternative medicine material. However, further research on teen tobacco use cessation programming in Russia with larger sample sizes, involving other locations of the country, and with stronger research designs is needed.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

Intervention with Substance-Abusing Runaway Adolescents and their Families: Results of a Randomized Clinical Trial. Slesnick N, Erdem G, Bartle-Haring S, Brigham GS. J Consult Clin Psychol. 2013 Aug; 81(4): 600-614.
The objectives of this study were to examine the efficacy of 3 theoretically distinct interventions among substance-abusing runaway adolescents and to explore individual differences in trajectories of change. Adolescents (N = 179) between the ages of 12 and 17 were recruited from a runaway shelter in a Midwestern city. The sample included 94 females (52.5%) and 85 males (47.5%); the majority of the adolescents were African American (n = 118, 65.9%). Adolescents were randomly assigned to the Community Reinforcement Approach (CRA, n = 57), Motivational Interviewing (MI, n = 61), or Ecologically-Based Family Therapy (EBFT, n = 61). Substance use was assessed at baseline, 3, 6, 9, 12, 18, and 24 months via Form 90 and urine screens. Hierarchical linear modeling revealed statistically significant improvement in frequency of substance use among runaways in all 3 treatment groups, with a slight increase at post-treatment. Latent trajectory profile analysis explored individual differences in change trajectories and yielded a 3-class model. The majority of adolescents (n = 136, 76%) showed reductions in substance use over time, with a slight increase at follow-up (Class 1: Decreasing). Twenty-four (13.4%) adolescents had shown high levels of substance use over time with patterns of increase and decrease (Class 2: Fluctuating high users), and 19 (10.6%) decreased but returned to baseline levels by 2 years postbaseline (Class 3: U shaped). Few differences among treatment conditions were noted; within the "decreasing" group, adolescents in MI treatment showed a quicker decline in their substance use but a faster relapse compared with those receiving EBFT. These findings suggest that CRA, EBFT, and MI are viable treatments for runaway substance-abusing adolescents.

Efficacy of Ecologically-Based Treatment with Substance-Abusing Homeless Mothers: Substance Use and Housing Outcomes. Slesnick N, Erdem G. J Subst Abuse Treat. 2013 Nov-Dec; 45(5): 416-425.
This randomized pilot study tested the efficacy of an integrative treatment targeting homeless substance abusing mothers with young children in their care. Sixty mothers with 2-6 year old children were recruited from a local family shelter. The mothers were randomly assigned to Ecologically-Based Treatment (n=30) or treatment as usual (n=30). The intervention group received 3 months of rental and utility assistance up to $600 per month, case management services, and substance abuse counseling (referred to as supportive services). The treatment as usual group received housing and services through the family shelter and community housing programs. All participants completed follow-up assessments at 3, 6, and 9 months post-baseline. Mothers receiving Ecologically-Based Treatment showed a quicker decline in alcohol frequency and a quicker increase in housing stability. Furthermore, with supportive services, two-thirds of women were successful in maintaining their apartments 6 months after rental assistance ended.

A Qualitative Analysis of Women's Experiences in Single-Gender versus Mixed-Gender Substance Abuse Group Therapy. Greenfield SF, Cummings AM, Kuper LE, Wigderson SB, Koro-Ljungberg M. Subst Use Misuse. 2013 Jun; 48(9): 750-760.
The present study of women with substance use disorders used grounded theory to examine women's experiences in both the Women's Recovery Group (WRG) and a mixed-gender Group

Drug Counseling (GDC). Semi-structured interviews were completed in 2005 by 28 women in a U.S. metropolitan area. Compared to GDC, women in WRG more frequently endorsed feeling safe, embracing all aspects of one's self, having their needs met, feeling intimacy, empathy, and honesty. In addition, group cohesion and support allowed women to focus on gender-relevant topics supporting their recovery. These advantages of single-gender group therapy can increase treatment satisfaction and improve treatment outcomes.

Parallel Demand-Withdraw Processes in Family Therapy for Adolescent Drug Abuse. Rynes KN, Rohrbaugh MJ, Lebensohn-Chialvo F, Shoham V. Psychol Addict Behav. 2013 Feb 25. [Epub ahead of print].

Isomorphism, or parallel process, occurs in family therapy when patterns of therapist-client interaction replicate problematic interaction patterns within the family. This study investigated parallel demand-withdraw processes in brief strategic family therapy (BSFT) for adolescent drug abuse, hypothesizing that therapist-demand/adolescent-withdraw interaction (TD/AW) cycles observed early in treatment would predict poor adolescent outcomes at follow-up for families who exhibited entrenched parent-demand/adolescent-withdraw interaction (PD/AW) before treatment began. Participants were 91 families who received at least four sessions of BSFT in a multisite clinical trial on adolescent drug abuse (Robbins et al., 2011). Prior to receiving therapy, families completed videotaped family interaction tasks from which trained observers coded PD/AW. Another team of raters coded TD/AW during two early BSFT sessions. The main dependent variable was the number of drug-use days that adolescents reported in timeline follow-back interviews 7 to 12 months after family therapy began. Zero-inflated Poisson regression analyses supported the main hypothesis, showing that PD/AW and TD/AW interacted to predict adolescent drug use at follow-up. For adolescents in high PD/AW families, higher levels of TD/AW predicted significant increases in drug use at follow-up, whereas for low PD/AW families, TD/AW and follow-up drug use were unrelated. Results suggest that attending to parallel demand-withdraw processes in parent-adolescent and therapist-adolescent dyads may be useful in family therapy for substance-using adolescents

Employment-Based Reinforcement of Adherence to Oral Naltrexone Treatment in Unemployed Injection Drug Users. Dunn KE, Defulio A, Everly JJ, Donlin WD, Aklin WM, Nuzzo PA, Leoutsakos JM, Umbricht A, Fingerhood M, Bigelow GE, Silverman K. Exp Clin Psychopharmacol. 2013 Feb; 21(1): 74-83.

Oral naltrexone has high potential for use as a relapse prevention pharmacotherapy for opiate dependence yet suffers from notoriously poor adherence. This study evaluated whether entry to a therapeutic workplace could reinforce adherence with oral naltrexone. Opiate-dependent and cocaine-using injection drug users were detoxified, inducted onto oral naltrexone, and randomly assigned to a contingency (n = 35) or prescription (n = 32) group for a 26-week period. Contingency participants were required to ingest naltrexone under staff observation to gain access to the therapeutic workplace. Prescription participants received a take-home supply of naltrexone and could access the workplace independent of naltrexone ingestion. Primary outcome measures were percent of urine samples positive for naltrexone at 30-day assessments and negative for opiates and cocaine at 30-day assessments. Contingency participants provided significantly more urine samples that were positive for naltrexone compared with prescription participants (72% vs. 21%, $p < .01$); however, no effect of experimental group was observed on percent opiate-negative (71% vs. 60%, $p = .19$.) or cocaine-negative (56% vs. 53%, $p = .82$)

samples in the contingency and prescription groups, respectively. Opiate-positive samples were significantly more likely to occur in conjunction with cocaine ($p < .001$) and when not protected by naltrexone ($p < .02$), independent of experimental group. Overall, these results show that contingent access to a therapeutic workplace significantly promoted adherence to oral naltrexone, and that the majority of opiate use occurred in conjunction with cocaine use, suggesting that untreated cocaine use may limit the effectiveness of oral naltrexone in promoting opiate abstinence.

Fatherhood and Intimate Partner Violence: Bringing the Parenting Role into Intervention Strategies. Stover CS, Morgos D. Prof Psychol Res Pr. 2013 Aug 1; 44(4): 247-256.
A large percentage of men who perpetrate intimate partner violence (IPV) are fathers who continue to live with or have visitation with their children. Yet, providers rarely consider that fathers who perpetrate IPV may benefit from a parent-child focused intervention. Therapeutic work with men, who perpetrate IPV, especially with their children, is complex with issues of child safety taking precedence. This article is meant to provide: 1) a rationale for considering father-child intervention in the context of IPV; 2) specific strategies for assessment; 3) guidelines for determining if a father is appropriate for such intervention; and 4) a review of treatment approaches that have been developed that may assist clinicians in work with this population.

Comparison of Youth, Caregiver, Therapist, Trained, and Treatment Expert Raters of Therapist Adherence to a Substance Abuse Treatment Protocol. Chapman JE, McCart MR, Letourneau EJ, Sheidow AJ. J Consult Clin Psychol. 2013 Aug; 81(4): 674-680.
This study evaluated the accuracy of youth, caregiver, therapist, and trained raters relative to treatment experts on ratings of therapist adherence to a substance abuse treatment protocol for adolescents. Adherence ratings were provided by youth and caregivers in an ongoing trial evaluating a Contingency Management (CM) intervention for youth in juvenile drug court. These ratings were compared to those provided by therapists and trained raters, and each rater type was compared to ratings provided by CM treatment experts. Data were analyzed using item-response-theory-based Many-Facet Rasch Models. Relative to treatment experts, youth and caregivers were significantly more likely to endorse the occurrence of CM components. In contrast, therapists and trained raters were much more consistent with treatment experts. In terms of practical significance, youth and caregivers each had a 97% estimated probability of indicating that a typical treatment component had occurred. By comparison, the probability was 31%, 19%, and 26% for therapists, trained raters, and treatment experts, respectively. The authors concluded that youth and caregivers were highly inaccurate relative to treatment experts, whereas, therapists and trained raters were generally consistent with treatment experts. The implications of these findings for therapist adherence measurement are considered.

Randomized Clinical Trial Examining Duration of Voucher-Based Reinforcement Therapy for Cocaine Abstinence. Kirby KC, Carpenedo CM, Dugosh KL, Rosenwasser BJ, Benishek LA, Janik A, Keashen R, Bresani E, Silverman K. Drug Alcohol Depend. 2013 Oct 1; 132(3): 639-645.
This is the first study to systematically manipulate duration of voucher-based reinforcement therapy (VBRT) to see if extending the duration increases abstinence during and following VBRT. The authors randomized cocaine-dependent methadone-maintained adults to Standard (12 weeks; n=62) or Extended (36 weeks; n=68) VBRT and provided escalating voucher

amounts contingent upon urinalysis verification of cocaine abstinence. Urinalysis was scheduled at least every 2 weeks during the 48-week study and more frequently during VBRT (3/week) and 12 weeks of Aftercare (2/week). Extended VBRT produced longer durations of continuous cocaine abstinence during weeks 1-24 (5.7 vs 2.7 weeks; p=0.003) and proportionally more abstinence during weeks 24-36 (X(2)=4.57, p=.03, OR=2.18) compared to Standard VBRT. Duration of VBRT did not directly predict after-VBRT abstinence; but longer continuous abstinence during VBRT predicted abstinence during Aftercare (p=0.001) and during the last 12 weeks of the study (p<0.001). Extended VBRT averaged higher monthly voucher costs compared to Standard VBRT ($96 vs $43, p<.001); however, the average cost per week of abstinence attained was higher in the Standard group ($8.06 vs $5.88, p<.001). Participants in the Extended group with voucher costs exceeding $25 monthly averaged 20 weeks of continuous abstinence. Greater abstinence occurred during Extended VBRT, but providing a longer duration was not by itself sufficient to maintain abstinence after VBRT. However, if abstinence can be captured and sustained during VBRT, then providing longer durations may help increase the continuous abstinence that predicts better long-term outcomes.

Engagement, Retention, and Abstinence for Three Types of Opioid Users in Florida. McCabe BE, Santisteban DA, Mena MP, Duchene DM, McLean C, Monroe M. Subst Use Misuse. 2013 Jun; 48(8): 623-634.
Prescription opioid use has grown rapidly, but few studies have examined whether users have similar treatment responses as heroin users. Participants were 1,648 opioid users in Florida Access to Recovery (2004-2007). Participants engaged in methadone or buprenorphine maintenance had better retention than those in nonmaintenance treatment. Heroin only users (HO) had better engagement in nonmaintenance treatments and had worse retention than prescription opioid only users (PO). In methadone maintenance, PO were more likely to report opioid abstinence during treatment than heroin and prescription opioid users (H&P). Future research should focus on understanding and improving the treatment experience of opioid use subgroups.

Opioid Abusers' Ability to Differentiate an Opioid from Placebo in Laboratory Challenge Testing. Antoine DG, Strain EC, Tompkins DA, Bigelow GE. Drug Alcohol Depend. 2013 Sep 1; 132(1-2): 369-372.
Abuse liability assessments influence drug development, federal regulation, and clinical care. One suggested procedure to reduce variability of assessments is a qualification phase, which assesses whether study applicants adequately distinguish active drug from placebo; applicants failing to make this distinction are disqualified. The present analyses assessed differences between qualification phase qualifiers and non-qualifiers. Data were collected from 23 completers of the qualification phase of an abuse liability study. Opioid abusing participants received 30 mg oxycodone and placebo orally on separate days, and were characterized as qualifiers (vs. non-qualifiers) if their peak visual analog scale liking rating for oxycodone was at least 20 points higher than placebo's peak rating. Groups were compared on demographic characteristics, drug history, and physiologic, subject and observer ratings. 61% of participants were qualifiers and 39% were non-qualifiers. Groups had similar demographic characteristics, drug use histories, and pupillary constriction responses. However, unlike qualifiers, non-qualifiers had an exaggerated placebo response for the liking score (p=0.03) and an attenuated oxycodone response for the liking score (p<0.0001). Non-qualifiers' failure to differentiate

oxycodone versus placebo was evident for subject and observer ratings. Different subjective responses to identical stimuli support the use of a qualification phase in abuse liability assessments. Further research should explore objective measures that may better account for these differences, determine optimal qualification criteria, and explore the developmental course of drug use. This study also documents certain opioid abusers fail to differentiate 30 mg of oxycodone from placebo, a phenomenon deserving further study.

Using Findings in Multimedia Learning to Inform Technology-Based Behavioral Health Interventions. Aronson ID, Marsch LA, Acosta MC. Transl Behav Med. 2013 Sep; 3(3): 234-243.
Clinicians and researchers are increasingly using technology-based behavioral health interventions to improve intervention effectiveness and to reach underserved populations. However, these interventions are rarely informed by evidence-based findings of how technology can be optimized to promote acquisition of key skills and information. At the same time, experts in multimedia learning generally do not apply their findings to health education or conduct research in clinical contexts. This paper presents an overview of some key aspects of multimedia learning research that may allow those developing health interventions to apply informational technology with the same rigor as behavioral science content. The authors synthesized empirical multimedia learning literature from 1992 to 2011. They identified key findings and suggested a framework for integrating technology with educational and behavioral science theory. A scientific, evidence-driven approach to developing technology-based interventions can yield greater effectiveness, improved fidelity, increased outcomes, and better client service.

Web-Based Behavioral Treatment for Substance Use Disorders as a Partial Replacement of Standard Methadone Maintenance Treatment. Marsch LA, Guarino H, Acosta M, Aponte-Melendez Y, Cleland C, Grabinski M, Brady R, Edwards J. J Subst Abuse Treat. 2014 Jan; 46(1): 43-51.
This study is the first experimental trial to evaluate the effectiveness of a Web-based behavioral intervention when deployed in a model where it partially substituted for standard counseling in a community-based specialty addiction treatment program. New opioid-dependent intakes in methadone maintenance treatment (n=160) were randomly assigned for 12months to either: (1) standard treatment or (2) reduced standard treatment plus a Web-based psychosocial intervention, the Therapeutic Education System (TES). Results demonstrated that replacing a portion of standard treatment with TES resulted in significantly greater rates of objectively measured opioid abstinence (48% vs. 37% abstinence across all study weeks; $F(1, 158)=5.90$, $p<.05$ and 59% vs. 43% abstinence on weeks participants provided urine samples for testing; $F(1, 158)=8.81$, $p<.01$). This result was robust and was evident despite how opioid abstinence was operationally defined and evaluated. The potential implications for service delivery models within substance abuse treatment programs and other healthcare entities are discussed.

Technology-Based Interventions for the Treatment and Recovery Management of Substance Use Disorders: A JSAT Special Issue. Marsch LA, Carroll KM, Kiluk BD. J Subst Abuse Treat. 2014 Jan; 46(1): 1-4.
A growing line of research has highlighted the promising role that interactive web and mobile technologies may play in improving the effectiveness, cost-effectiveness, and reach of efforts to assess, prevent, treat, and support the recovery management of substance use disorders and other

risk behavior. Manuscripts in this special issue of the Journal of Substance Abuse Treatment focus on the application of technology to the delivery of interventions for the treatment and recovery management of substance use disorders. These manuscripts are intended to highlight the diversity and current state of the science of empirically-supported innovations in this area of intervention delivery. The included manuscripts range from experimental evaluations of a variety of types of technology-based interventions (brief interventions, behavior therapy, medication adherence tools, and HIV prevention interventions) and technology platforms (mobile, Web, videoconferencing, and telephone-based interactive voice response), for an array of populations (adults, adolescents, criminal justice populations, and post-partum women), in a number of different settings (addiction specialty treatment programs, schools, emergency rooms, and criminal justice settings). They additionally reflect a variety of experimental research designs, including those focused on the design, development, and clinical evaluation of these technology-based therapeutic tools, as well as research focused on models for their successful implementation and sustained use.

Feasibility of Delivering Evidence-Based HIV/STI Prevention Programming to a Community Sample of African American Teen Girls via the Internet. Danielson CK, McCauley JL, Jones AM, Borkman AL, Miller S, Ruggiero KJ. AIDS Educ Prev. 2013 Oct; 25(5): 394-404.
The current study examined the feasibility of an HIV/STI prevention intervention for African American female adolescents. The intervention SiHLEWeb is a web-based adaptation of the evidence-based intervention, Sistas, Informing, Healing, Living, and Empowering (SiHLE). Participants were 41 African American girls aged 13 to 18 years, recruited in collaboration with community partners (local high schools, Department of Juvenile Justice, child advocacy center, medical university). Results support the feasibility of recruitment, screening, and follow-up retention methods. The majority (63.4%) of recruited participants completed the intervention, taking an average of 4.5 (SD = 3.63) site visits. Completers of SiHLEWeb demonstrated increases in knowledge regarding HIV/STI risks and risk reduction behavior [$t(18) = 4.74$, $p < .001$], as well as significant increases in condom use self-efficacy [$t(16) = 2.41$, $p = .03$]. Findings provide preliminary support for the large-scale, randomized-controlled trial of the efficacy of SiHLEWeb to reduce high-risk sexual behavior among female African American adolescents.

College Cannabis Use: The Unique Roles of Social Norms, Motives, and Expectancies. Buckner JD. J Stud Alcohol Drugs. 2013 Sep; 74(5): 720-726.
Given that the majority of college cannabis use occurs in social situations, descriptive norms (beliefs about others' use) and injunctive norms (others' approval of risky use) may be particularly relevant to cannabis-related behaviors. Yet, little research has examined the unique impact of these norms on one's own behaviors when accounting for the variance attributable to other relevant cognitive factors. The current study is the first known investigation of the unique impact of social norms, cannabis use motives, and cannabis effect expectancies on cannabis use. Data came from 223 (64.1% female) current cannabis-using undergraduates who completed an online questionnaire in exchange for psychology-course research credit. Descriptive norms regarding friends (not students in general) and injunctive norms (friends and parents) were related to cannabis use frequency. Descriptive norms (friends, not students in general) and injunctive norms (friends, not parents) were related to cannabis problems. Relevant norms,

expectancies, and motives accounted for 66.8% of the variance in cannabis use frequency and 28.7% of the variance in cannabis problems. In multivariate analyses, descriptive norms (friends) accounted for the greatest amount of unique variance in cannabis use frequency, whereas coping motives accounted for the greatest amount of unique variance in cannabis-related problems. Descriptive norms (friends) and coping motives may be two cognitive vulnerability factors that could be particularly important targets for interventions.

Changes in Post-Traumatic Stress Symptoms among Women in Substance Use Disorder Treatment: The Mediating Role of Bodily Dissociation and Emotion Regulation. Price CJ, Herting JR. Substance Abuse: Research and Treatment 2013; 7: 147–153.
Individuals in substance use disorder (SUD) treatment have shown high levels of difficulty with emotion regulation, as well as a high prevalence of reported trauma and symptoms of post-traumatic stress (PTS). Dissociation from the body is a common clinical experience among women with a history of sexual trauma. Research has shown promising effects of mind-body approaches in SUD treatment, as well as the importance of emotional regulation in conceptual models of psychopathology. The current study examines the mediating role of bodily dissociation and emotion regulation on PTS symptoms in a sample of women enrolled in substance use disorder treatment. Results indicate that bodily dissociation and emotion regulation had significant direct effects on PTS symptoms from baseline to a 6-month follow-up, and that bodily dissociation also may indirectly operate to reduce PTS symptoms through its effect on emotion regulation difficulties. These results suggest the importance of addressing bodily dissociation and emotion regulation difficulties in women's substance use disorder treatment.

A Randomized Double-blind Evaluation of Buprenorphine Taper Duration in Primary Prescription Opioid Abusers. Sigmon SC, Dunn KE, Saulsgiver K, Patrick ME, Badger GJ, Heil SH, Brooklyn JR, Higgins ST. 2013 Oct 23. doi: 10.1001/jamapsychiatry.2013.2216. [Epub ahead of print].
Although abuse of prescription opioids (POs) is a significant public health problem, few experimental studies have investigated the treatment needs of this growing population. The objective of this study was to evaluate, following brief stabilization with a combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate, the relative efficacy of 1-, 2-, and 4-week buprenorphine tapering regimens and subsequent naltrexone hydrochloride therapy in PO-dependent outpatients. A double-blind, 12-week randomized clinical trial was conducted in an outpatient research clinic. Following a brief period of buprenorphine stabilization, 70 PO-dependent adults were randomized to receive 1-, 2-, or 4-week tapers followed by naltrexone therapy. During phase 1 (weeks 1-5 after randomization), participants visited the clinic daily; during phase 2 (weeks 6-12), visits were reduced to thrice weekly. Participants received behavioral therapy and urine toxicology testing throughout the trial. Main outcome measures included the percentage of participants negative for illicit opioid use, retention, naltrexone ingestion, and favorable treatment response (i.e., retained in treatment, opioid abstinent, and receiving naltrexone at the end of the study). Opioid abstinence at the end of phase 1 was greater in the 4-week compared with the 2- and 1-week taper conditions ($p = .02$), with 63% ($n = 14$), 29% ($n = 7$), and 29% ($n = 7$) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. Abstinence at the end of phase 2 was also greater in the 4-week compared with the 2- and 1-week conditions ($p = .03$), with 50% ($n = 11$), 16% ($n = 4$), and 20% ($n = 5$) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. There were

more treatment responders in the 4-week condition (p = .03), with 50% (n = 11), 17% (n = 4), and 21% (n = 5) of participants in the 4-, 2-, and 1-week groups considered responders at the end of treatment, respectively. Retention and naltrexone ingestion also were superior in the 4-week vs briefer tapers (both P = .04). Experimental condition (i.e., taper duration) was the strongest predictor of treatment response, followed by buprenorphine stabilization dose. This study represents a rigorous experimental evaluation of outpatient buprenorphine stabilization, brief taper, and naltrexone maintenance for treatment of PO dependence. Results suggest that a meaningful subset of PO-dependent outpatients may respond positively to a 4-week taper plus naltrexone maintenance intervention.

An Adaptive Approach for Identifying Cocaine Dependent Patients who Benefit from Extended Continuing Care. McKay JR, Van Horn DH, Lynch KG, Ivey M, Cary MS, Drapkin ML, Coviello DM, Plebani JG. J Consult Clin Psychol. 2013 Sep 16. [Epub ahead of print]. This study tested whether cocaine dependent patients using cocaine or alcohol at intake or in the first few weeks of intensive outpatient treatment would benefit more from extended continuing care than patients abstinent during this period. The effect of incentives for continuing care attendance was also examined. Participants (N = 321) were randomized to treatment as usual (TAU), TAU and telephone monitoring and counseling (TMC), or TAU and TMC plus incentives (TMC+). The primary outcomes were (a) abstinence from all drugs and heavy alcohol use and (b) cocaine urine toxicology. Follow-ups were at 3, 6, 9, 12, 18, and 24 months. Cocaine and alcohol use at intake or early in treatment predicted worse outcomes on both measures (ps ≤ .0002). Significant effects favoring TMC over TAU on the abstinence composite were obtained in participants who used cocaine (odds ratio [OR] = 1.95 [1.02, 3.73]) or alcohol (OR = 2.47 [1.28, 4.78]) at intake or early in treatment. A significant effect favoring TMC+ over TAU on cocaine urine toxicology was obtained in those using cocaine during that period (OR = 0.55 [0.31, 0.95]). Conversely, there were no treatment effects in participants abstinent at baseline and no overall treatment main effects. Incentives almost doubled the number of continuing care sessions received but did not further improve outcomes. An adaptive approach for cocaine dependence in which extended continuing care is provided only to patients who are using cocaine or alcohol at intake or early in treatment improves outcomes in this group while reducing burden and costs in lower risk patients.

Neurocognitive Functioning of Individuals with Schizophrenia: Using and Not Using Drugs. Bahorik AL, Newhill CE, Eack SM.Schizophr Bull. 2013 Sep 11. [Epub ahead of print]. Research on neurocognition in schizophrenia, using modest samples and self-rated assessments, reports drug use contributes to improved rather than impaired cognitive function. The authors have sought to replicate these findings in a large sample of patients that had their drug-use status confirmed by laboratory assays and evaluated the potential differences in cognitive function between patients with positive and negative results. Nine hundred and seventy four schizophrenia patients completed neuropsychological and laboratory tests at screening/baseline of the Clinical Antipsychotic Trials of Intervention Effectiveness study. Radioimmunoassay (RIA) of hair tested for cannabis, cocaine and methamphetamine. Many patients screened positive for drug use (n = 262; 27%), and there were no differences between patients with positive and negative results in terms of cognitive function after adjusting for multiple inference testing, except patients with positive RIA for methamphetamine demonstrated increased processing speed (corrected, P = .024). Moderator models were employed to explore potential

subgroup differences in this pattern of results. At low medication dosages, patients with positive RIA for cocaine demonstrated decreased processing speed compared with patients with negative RIA for cocaine (uncorrected, P = .008). And for any other drugs with low psychopathology, patients with positive RIA demonstrated decreased working memory compared with patients with negative RIA (uncorrected, P = .006). No positive effects of cannabis on cognitive function were observed, and drug use was not associated with improved neurocognition across most of the subgroup characteristics explored in this sample of schizophrenia patients.

Prefrontal Cortical Dysfunction during Visual Perspective-Taking in Schizophrenia. Eack SM, Wojtalik JA, Newhill CE, Keshavan MS, Phillips ML. Schizophr Res. 2013 Nov; 150(2-3): 491-497. doi: 10.1016/j.schres.2013.08.022. Pub 2013 Sep 19. [Epub ahead of print].
Schizophrenia is characterized by marked impairments in a broad and diverse array of social-cognitive domains. Fundamental deficits in the ability to visualize and shift to the perspectives of others and the neural networks that support this ability may contribute to many of these impairments. This study sought to investigate deficits in prefrontal brain function and connectivity in patients with schizophrenia during visual perspective-taking, and the degree to which such deficits contribute to higher-order impairments in social cognition. A total of 20 outpatients with schizophrenia and 20 age- and gender-matched healthy volunteers completed a basic, visual perspective-taking task during functional magnetic resonance imaging, along with a behavioral assessment of theory of mind after neuroimaging. Results revealed hypoactivity in the medial prefrontal (anterior cingulate) and orbitofrontal cortices during perspective-taking trials compared to control trials in schizophrenia patients relative to healthy controls. In addition, patients demonstrated significant deficits in negative connectivity between medial prefrontal and medial-temporal regions during perspective-taking, which fully mediated behavioral impairments observed in theory of mind. These findings suggest that disruptions are present in the most fundamental aspects of perspective-taking in schizophrenia, and that these disruptions impact higher-order social information processing.

A Randomized Clinical Trial of Smoking Cessation Treatments Provided in HIV Clinical Care Settings. Humfleet GL, Hall SM, Delucchi KL, Dilley JW. Nicotine Tob Res. 2013 Aug; 15(8): 1436-1445.
Identifying successful smoking treatment interventions and methods of delivery is critical given the smoking rates among HIV-positive populations and the medical implications of smoking in this population. This study compared the efficacy of 3 smoking cessation interventions provided in HIV clinical treatment settings. Following a baseline assessment, 209 HIV-positive smokers were randomly assigned to 1 of 3 conditions in a parallel group design. Treatment conditions were individual counseling plus nicotine replacement treatment (NRT), a computer-based Internet smoking treatment plus NRT, and self-help plus NRT. Smoking status was determined at follow-up assessments completed at 12, 24, 36, and 52 weeks following treatment initiation. Cessation rates ranged from 15% to 29%; however, no statistically significant differences in abstinence were found among the treatment conditions over time. Those employed, those who reported a greater desire to quit, or those with lower mood disturbance scores were more likely to achieve abstinence ($p < .01$). The number of cigarettes participants reported smoking in the 24hr prior to each assessment significantly declined over time ($p < .001$). Although the authors found no differences in abstinence rates across groups, the results indicate that integration of smoking cessation interventions is feasible in HIV clinical treatment settings, and cessation results are

promising. The overall abstinence rates the authors report are comparable to those found in similar treatment studies across multiple populations. Further research is warranted.

Real-Time fMRI Links Subjective Experience with Brain Activity during Focused Attention. Garrison KA, Scheinost D, Worhunsky PD, Elwafi HM, Thornhill TA 4th, Thompson E, Saron C, Desbordes G, Kober H, Hampson M, Gray JR, Constable RT, Papademetris X, Brewer JA. Neuroimage. 2013 Nov 1; 81: 110-118.
Recent advances in brain imaging have improved the measure of neural processes related to perceptual, cognitive and affective functions, yet the relation between brain activity and subjective experience remains poorly characterized. In part, it is a challenge to obtain reliable accounts of participant's experience in such studies. Here the authors addressed this limitation by utilizing experienced meditators who are expert in introspection. They tested a novel method to link objective and subjective data, using real-time fMRI (rt-fMRI) to provide participants with feedback of their own brain activity during an ongoing task. They provided real-time feedback during a focused attention task from the posterior cingulate cortex, a hub of the default mode network shown to be activated during mind-wandering and deactivated during meditation. In a first experiment, both meditators and non-meditators reported significant correspondence between the feedback graph and their subjective experience of focused attention and mind-wandering. When instructed to volitionally decrease the feedback graph, meditators, but not non-meditators, showed significant deactivation of the posterior cingulate cortex. The authors were able to replicate these results in a separate group of meditators using a novel step-wise rt-fMRI discovery protocol in which participants were not provided with prior knowledge of the expected relationship between their experience and the feedback graph (i.e., focused attention versus mind-wandering). These findings support the feasibility of using rt-fMRI to link objective measures of brain activity with reports of ongoing subjective experience in cognitive neuroscience research, and demonstrate the generalization of expertise in introspective awareness to novel contexts.

An Exploratory Randomized Controlled Trial of a Novel High-School-Based Smoking Cessation Intervention for Adolescent Smokers Using Abstinence-Contingent Incentives and Cognitive Behavioral Therapy. Krishnan-Sarin S, Cavallo DA, Cooney JL, Schepis TS, Kong G, Liss TB, Liss AK, McMahon TJ, Nich C, Babuscio T, Rounsaville BJ, Carroll KM. Drug Alcohol Depend. 2013 Sep 1; 132(1-2): 346-351.
There are few effective smoking cessation interventions for adolescent smokers. The authors developed a novel intervention to motivate tobacco use behavior change by (1) enhancing desire to quit through the use of abstinence-contingent incentives (CM), (2) increasing cessation skills through the use of cognitive behavioral therapy (CBT), and (3) removing cessation barriers through delivery within high schools. An exploratory four-week, randomized controlled trial was conducted in Connecticut high schools to dismantle the independent and combined effects of CM and CBT; smokers received CM alone, CBT alone, or CM+CBT. Participants included 82 adolescent smokers seeking smoking cessation treatment. The primary outcome was seven-day end-of-treatment (EOT) point prevalence (PP) abstinence, determined using self-reports confirmed using urine cotinine levels. Secondary outcomes included one-day EOT PP abstinence and cigarette use during treatment and follow up. Among participants who initiated treatment (n=72), group differences in seven-day EOT-PP abstinence were observed ($\chi(2)=10.48$, $p<0.01$) with higher abstinence in the CM+CBT (36.7%) and CM (36.3%) conditions when compared

with CBT (0%). One-day EOT-PP abstinence evidenced similar effects ($\chi(2)=10.39$, $p<0.01$; CM+CBT: 43%, CM: 43%, CBT: 4.3%). Survival analyses indicated differences in time to first cigarette during treatment ($\chi(2)=8.73$, $p=0.003$; CBT: Day 3, CM: Day 9, CM+CBT: Day 20). At one- and three-month follow ups, while no differences were observed, the CM alone group had the slowest increase in cigarette use. High-school, incentive-based smoking cessation interventions produce high rates of short-term abstinence among adolescent smokers; adding cognitive behavioral therapy does not appear to further enhance outcomes.

Reinforcing Integrated Psychiatric Service Attendance in an Opioid-Agonist Program: A Randomized and Controlled Trial. Kidorf M, Brooner RK, Gandotra N, Antoine D, King VL, Peirce J, Ghazarian S. Drug Alcohol Depend. 2013 Nov 1; 133(1): 30-36.
The benefits of integrating substance abuse and psychiatric care may be limited by poor service utilization. This randomized clinical trial evaluated the efficacy of using contingency management to improve utilization of psychiatric services co-located and integrated within a community-based methadone maintenance treatment program. Opioid-dependent outpatients (n=125) with any current psychiatric disorder were randomly assigned to: (1) reinforced on-site integrated care (ROIC), with vouchers (worth $25.00) contingent on full adherence to each week of scheduled psychiatric services; or (2) standard on-site integrated care (SOIC). All participants received access to the same schedule of psychiatrist and mental health counseling sessions for 12-weeks. ROIC participants attended more overall psychiatric sessions at month 1 (M=7.53 vs. 3.97, p<.001), month 2 (M=6.31 vs. 2.81, p<.001), and month 3 (M=5.71 vs. 2.44, p<.001). Both conditions evidenced reductions in psychiatric distress (p<.001) and similar rates of drug-positive urine samples. No differences in study retention were observed. These findings suggest that contingency management can improve utilization of psychiatric services scheduled within an on-site and integrated treatment model. Delivering evidenced-based mental health counseling, or modifying the contingency plan to include illicit drug use, may be required to facilitate greater changes in psychiatric and substance abuse outcomes.

Acceptability of Contingency Management among Clinicians and Clients within a Co-occurring Mental Health and Substance Use Treatment Program. Srebnik D, Sugar A, Coblentz P, McDonell MG, Angelo F, Lowe JM, Ries RK, Roll J. Am J Addict. 2013 Sep-Oct; 22(5): 432-436.
Emerging evidence supports the effectiveness of contingency management (CM) for addictions treatment among individuals with co-occurring serious mental illness (SMI). Addiction treatment for people with SMI generally occurs within community mental health centers (CMHCs) and it is not known whether CM is acceptable within this context. Client views regarding CM are also unknown. This study is the first to describe CM acceptability among CMHC clinicians, and the first to explore client views. Clinician-level predictors of CM acceptability are also examined. This study examined views about CM among 80 clinicians and 29 clients within a CMHC within the context of a concurrent CM study. Three-quarters of clinicians reported they would use CM if funding were available. Clinicians and clients affirmed that incentives enhance abstinence motivation. Clinician CM acceptability was related to greater years of experience, and identifying as an addictions or co-occurring disorders counselor, more than a mental health clinician. These findings provide preliminary evidence that CMHC clinicians, serving clients with addictions and complicating SMI, and client participants in CM, view CM as motivating

and a positive tool to facilitate recovery. The authors conclude that as an evidence-based intervention, CM warrants further efforts toward funding and dissemination in CMHCs.

Perceived Partner Responsiveness Predicts Decreases in Smoking during the First Nine Years of Marriage. Derrick JL, Leonard KE, Homish GG. Nicotine Tob Res. 2013 Sep; 15(9): 1528-1536.
Support for quitting is associated with smoking cessation, but few studies have examined the influence of more general social support on smoking outcomes. The current research examines perceptions of the partner's willingness and ability to provide general social support (i.e., perceived partner responsiveness) as a longitudinal predictor of smoking trajectories. Data are from a sample of newlywed couples assessed at six timepoints over 9 years. The current analyses focus on both partners in 333 "ever-smoker" couples. Participants completed measures of partner responsiveness, smoking, and demographics through the mail at each timepoint. Both husbands and wives who initially reported greater partner responsiveness showed a decrease over the following 9 years in the likelihood of being a smoker and in cigarette quantity. This decrease was not apparent for husbands and wives who initially reported lower partner responsiveness. These effects were mediated by several time-varying characteristics. Previous research has shown that support for quitting is an important predictor of smoking cessation. The current research demonstrates that more general perceived social support, unrelated to smoking behavior, also predicts decreases in smoking over time in both men and women. In fact, reports of partner responsiveness at baseline predicted smoking over 9 years, demonstrating the potency of this particular relationship perception for smoking outcomes.

An Exploratory Pilot Study of the Relationship between Neural Correlates of Cognitive Control and Reduction in Cigarette Use among Treatment-Seeking Adolescent Smokers. Krishnan-Sarin S, Balodis IM, Kober H, Worhunsky PD, Liss T, Xu J, Potenza MN. Psychol Addict Behav. 2013 Jun; 27(2): 526-532.
Despite high rates of tobacco use during adolescence, few empirically validated smoking cessation strategies exist for adolescent smokers. Developing an understanding of the neural underpinnings of cognitive control processes in adolescent smokers, and their relationship to quit behaviors, may help advance the development of enhanced behavioral and pharmacological therapies. The current pilot study explored the relationship between brain responses during performance of the Stroop color-word interference task and reduction in tobacco use (as measured by changes in cotinine levels) in treatment-seeking adolescent smokers participating in a high school-based smoking-cessation program. Eleven adolescent daily smokers participated in a prequit session during which neural activity in response to congruent and incongruent events in a Stroop task was examined using functional MRI (fMRI). Changes in urine cotinine levels from prequit baseline to end of treatment were calculated and correlated with brain activity. Adolescents with greater activation in the inferior frontal gyrus, insula, thalamus, and anterior cingulate had greater reductions in cotinine levels. The preliminary observation of a relationship between treatment outcome and neural correlates of cognitive control prior to treatment onset provides insight into individual differences in adolescent brain function that might relate importantly to treatment outcome.

Efficacy of Initiating Tobacco Dependence Treatment in Inpatient Psychiatry: A Randomized Controlled Trial. Prochaska JJ, Hall SE, Delucchi K, Hall SM. Am J Public Health. 2013 Aug 15. [Epub ahead of print].
The authors evaluated the efficacy of a motivational tobacco cessation treatment combined with nicotine replacement relative to usual care initiated in inpatient psychiatry. They randomized participants (n = 224; 79% recruitment rate) recruited from a locked acute psychiatry unit with a 100% smoking ban to intervention or usual care. Prior to hospitalization, participants averaged 19 (SD = 12) cigarettes per day; only 16% intended to quit smoking in the next 30 days. Verified smoking 7-day point prevalence abstinence was significantly higher for intervention than usual care at month 3 (13.9% vs 3.2%), 6 (14.4% vs 6.5%), 12 (19.4% vs 10.9%), and 18 (20.0% vs 7.7%; odds ratio [OR] = 3.15; 95% confidence interval [CI] = 1.22, 8.14; P = .018; retention > 80%). Psychiatric measures did not predict abstinence; measures of motivation and tobacco dependence did. The usual care group had a significantly greater likelihood than the intervention group of psychiatric rehospitalization (adjusted OR = 1.92; 95% CI = 1.06, 3.49). These findings support initiation of motivationally tailored tobacco cessation treatment during acute psychiatric hospitalization. Psychiatric severity did not moderate treatment efficacy, and cessation treatment appeared to decrease rehospitalization risk, perhaps by providing broader therapeutic benefit.

Development and Preliminary Randomized Controlled Trial of a Distress Tolerance Treatment for Smokers with a History of Early Lapse. Brown RA, Reed KM, Bloom EL, Minami H, Strong DR, Lejuez CW, Kahler CW, Zvolensky MJ, Gifford EV, Hayes SC. Nicotine Tob Res. 2013 Dec; 15(12): 2005-2015.
An inability to tolerate distress is a significant predictor of early smoking lapse following a cessation attempt. The authors conducted a preliminary randomized controlled trial to compare a distress tolerance (DT) treatment that incorporated elements of exposure-based therapies and Acceptance and Commitment Therapy to standard smoking cessation treatment (ST). Smokers with a history of early lapse in prior quit attempts received either DT (N = 27; 9 2-hr group and 6 50-min individual sessions) or ST (N = 22; 6 90-min group and 1 20-min individual session), plus 8 weeks of transdermal nicotine patch. At the end of behavioral treatment, odds of abstinence among participants receiving DT were 6.46 times greater than among participants receiving ST (66.7% vs. 31.8%), equivalent to a medium- to large-effect size. Odds of abstinence for DT were still 1.73 times greater at 8 weeks, corresponding to a small- to medium-effect size, although neither this difference nor those at 13 and 26 weeks were statistically significant. Furthermore, of those who lapsed to smoking during the first week postquit, DT participants had more than 4 times greater odds of abstinence than ST participants at the end of treatment. Relative to ST, DT participants also reported a larger decrease in experiential avoidance, a hypothesized DT treatment mediator, prior to quit day. The trajectory of negative mood and withdrawal symptoms in DT differed from ST and was largely consistent with hypotheses. Reasons for the decrease in abstinence in DT after treatment discontinuation and suggestions for future research are discussed.

The Recovery Line: A Pilot Trial of Automated, Telephone-Based Treatment for Continued Drug Use in Methadone Maintenance. Moore BA, Fazzino T, Barry DT, Fiellin DA, Cutter CJ, Schottenfeld RS, Ball SA. J Subst Abuse Treat. 2013 Jul; 45(1): 63-69.
The current pilot study evaluated feasibility, acceptability, and initial efficacy of a therapeutic Interactive Voice Response (IVR) system ("the Recovery Line") for patients receiving methadone maintenance who continue to use illicit drugs. Patients were randomized (N=36) to 4weeks of treatment-as-usual (TAU) or Recovery Line plus TAU. Ratings of the Recovery Line were high and remained stable throughout the study. However, despite instructions and reminders, patients used substantially less than the recommended daily use (<10 days of 28). Patients were more likely to report abstinence from opioids and cocaine on days they used the Recovery Line (p=.01) than those they did not. Conditions did not differ significantly on patient satisfaction, urine screen outcomes, or coping efficacy. As with other computer-based treatments, findings suggest the Recovery Line is acceptable and feasible. However, additional methods to increase patient utilization of automated systems and larger clinical trials are needed.

Pilot Randomized Controlled Trial of Web-Based Acceptance and Commitment Therapy for Smoking Cessation. Bricker J, Wyszynski C, Comstock B, Heffner JL. Nicotine Tob Res. 2013 Oct; 15(10): 1756-1764.
Web-based smoking cessation interventions have high reach, but low effectiveness. To address this problem, the authors conducted a pilot randomized controlled trial of the first web-based acceptance and commitment therapy (ACT) intervention for smoking cessation. The aims were to determine design feasibility, user receptivity, effect on 30-day point prevalence quit rate at 3 months post-randomization, and mediation by ACT theory-based processes of acceptance. Adult participants were recruited nationally into the double-blind randomized controlled pilot trial (N = 222), which compared web-based ACT for smoking cessation (WebQuit.org) with the National Cancer Institute's Smokefree.gov-the U.S. national standard for web-based smoking cessation interventions. The authors recruited 222 participants in 10 weeks. Participants spent significantly longer on the ACT WebQuit.org site per login (18.98 vs. 10.72 min; p = .001) and were more satisfied with the site (74% vs. 42%; p =.002). Using available follow-up data, more than double the fraction of participants in the ACT WebQuit.org arm had quit smoking at the 3-month follow-up (23% vs. 10%; OR = 3.05; 95% CI = 1.01-9.32; p = .050). Eighty percent of this effect was mediated by ACT theory-based increases in total acceptance of physical, cognitive, and emotional cues to smoke (p < .001). Compared with Smokefree.gov, ACT had higher user receptivity and short-term cessation, and strong evidence of theory-based mechanisms of change. While results were promising, they were limited by the pilot design (e.g., limited follow-up), and thus a full-scale efficacy trial is now being conducted.

Marijuana Use is Associated with Risky Sexual Behaviors in Treatment-Seeking Polysubstance Abusers. Andrade LF, Carroll KM, Petry NM. Am J Drug Alcohol Abuse. 2013 Jul 39; (4): 266-271.
Multiple types of substance use are associated with HIV risk behaviors, but relatively little research has examined the association between marijuana use and risky sexual activities in treatment-seeking polysubstance abusing patients. This study evaluated the relationship between marijuana use and sexual behaviors in 239 patients with cocaine, opioid or alcohol use disorders who were initiating outpatient substance use treatment. Participants completed the HIV Risk Behavior Scale and were classified into one of three groups based on their marijuana use

histories: never (n = 66), past but not current use (n = 124) or current use (n = 49). Compared to never marijuana users, current and former marijuana users had a greater likelihood of having more than 50 lifetime sexual partners (odds ratio [OR] and 95% confidence interval [CI] = 3.9 [1.0-15.7] and 5.2 [1.6-17.3], respectively). Former marijuana users had increased risk of low frequency condom use with casual partners relative to never users (OR [95% CI] = 2.9 [1.1-7.6]). Moreover, current marijuana users were more likely than never users to have had more than two recent sexual partners (OR [95% CI] = 8.1 [1.94-33.44]). Treatment-seeking polysubstance abusers with current or past marijuana use histories may be at greater risk of HIV infection than their counterparts who do not use marijuana. These data underscore the importance of increasing awareness about the potential association between marijuana use and increased high-risk sexual behavior among polysubstance abusing patients.

Influence of a Dopamine Pathway Additive Genetic Efficacy Score on Smoking Cessation: Results from Two Randomized Clinical Trials of Bupropion. David SP, Strong DR, Leventhal AM, Lancaster MA, McGeary JE, Munafò MR, Bergen AW, Swan GE, Benowitz NL, Tyndale RF, Conti DV, Brown RA, Lerman C, Niaura R. Addiction. 2013 Dec; 108(12): 2202-2211.

The aims of this study were to evaluate the associations of treatment and an additive genetic efficacy score (AGES) based on dopamine functional polymorphisms with time to first smoking lapse and point prevalence abstinence at end of treatment among participants enrolled into two randomized clinical trials of smoking cessation therapies. These were double-blind pharmacogenetic efficacy trials randomizing participants to active or placebo bupropion. Study 1 also randomized participants to cognitive–behavioral smoking cessation treatment (CBT) or this treatment with CBT for depression. Study 2 provided standardized behavioural support. The study settings were two hospital-affiliated clinics (study 1), and two university-affiliated clinics (study 2). Participants comprised a total of 792 self-identified white treatment-seeking smokers aged ≥18 years smoking ≥10 cigarettes per day over the last year. Measurements obtained included age, gender, Fagerström Test for Nicotine Dependence, dopamine pathway genotypes (rs1800497 [ANKK1 E713K], rs4680 [COMT V158M], DRD4 exon 3 variable number of tandem repeats polymorphism [DRD4 VNTR], SLC6A3,3′ VNTR) analyzed both separately and as part of an AGES, time to first lapse and point prevalence abstinence at end of treatment. Significant associations of the AGES (hazard ratio [HR] = 1.10, 95% confidence interval [CI] = 1.06–1.14, P = 0.009) and of the DRD4 VNTR (HR = 1.29, 95% CI = 1.17–1.41, P = 0.0073) were observed with time to first lapse. A significant AGES by pharmacotherapy interaction was observed (β standard error = −0.18 [0.07], P = 0.016), such that AGES predicted risk for time to first lapse only for individuals randomized to placebo. The authors conclude that a score based on functional polymorphisms relating to dopamine pathways appears to predict lapse to smoking following a quit attempt, and the association is mitigated in smokers using bupropion.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Immunogenicity Of Individual Vaccine Components In A Bivalent Nicotine Vaccine Differ According To Vaccine Formulation and Administration Conditions. Cornish KE, de Villiers SH, Pravetoni M, Pentel PR. PLoS One. 2013 Dec 2; 8(12): e82557.
Structurally distinct nicotine immunogens can elicit independent antibody responses against nicotine when administered concurrently. Co-administering different nicotine immunogens together as a multivalent vaccine could be a useful way to generate higher antibody levels than with monovalent vaccines alone. The immunogenicity and additivity of monovalent and bivalent nicotine vaccines was studied across a range of immunogen doses, adjuvants, and routes to assess the generality of this approach. Rats were vaccinated with total immunogen doses of 12.5 - 100 μg of 3'-aminomethyl nicotine conjugated to recombinant Pseudomonas exoprotein A (3'-AmNic-rEPA), 6-carboxymethylureido nicotine conjugated to keyhole limpet hemocyanin (6-CMUNic-KLH), or both. Vaccines were administered s.c. in alum or i.p. in Freund's adjuvant at matched total immunogen doses. When administered s.c. in alum, the contributions of the individual immunogens to total nicotine-specific antibody (NicAb) titers and concentrations were preserved across a range of doses. Antibody affinity for nicotine varied greatly among individuals but was similar for monovalent and bivalent vaccines. However when administered i.p. in Freund's adjuvant the contributions of the individual immunogens to total NicAb titers and concentrations were compromised at some doses. These results support the possibility of co-administering structurally distinct nicotine immunogens to achieve a more robust immune response than can be obtained with monovalent immunogens alone. Choice of adjuvant was important for the preservation of immunogen component activity.

Increased Efficacy Of A Trivalent Nicotine Vaccine Compared To A Dose-Matched Monovalent Vaccine When Formulated With Alum. Villiers SH, Cornish KE, Troska AJ, Pravetoni M, Pentel PR. Vaccine. 2013 Dec 16; 31(52): 6185-6193.
Vaccination against nicotine is a potential treatment for tobacco smoking. Clinical trials show effect only in high antibody responders; therefore it is necessary to increase the effectiveness of nicotine vaccines. The use of a multivalent vaccine that activates several B cell populations is a possible approach to increase antibody response. The aim of this study was to investigate whether three different nicotine immunogens could be mixed to generate independent responses resulting in additive antibody titers, and whether this would alter nicotine distribution to a greater extent than antibodies generated by a monovalent vaccine. When immunogens were administered s.c. with alum adjuvant, the trivalent vaccine generated significantly higher titers and prevented the distribution of an i.v. nicotine dose to brain to a greater extent than an equivalent dose of a monovalent vaccine. The number of rats with antibody titers >1:10,000 was significantly increased in the trivalent group compared to the monovalent group. There were no correlations between the titers generated by the different nicotine immunogens in the trivalent vaccine, supporting the hypothesis that the immunogens generated independent responses from distinct populations of B cells. In contrast, when administered i.p. in Freund's adjuvant, the trivalent nicotine vaccine was not more immunogenic than its component monovalent vaccine. Vaccine immunogenicity was suppressed if unconjugated protein was added to the monovalent vaccine formulated in Freund's adjuvant, compared to monovalent vaccine alone. These data suggest a protein-protein interaction that affects titers negatively and is apparent when the vaccines are formulated with Freund's adjuvant. In summary, a trivalent nicotine vaccine

formulated with alum showed significantly higher efficacy than a dose-matched monovalent vaccine and may offer a strategy for increasing nicotine vaccine immunogenicity. This approach may be generalizable to other nicotine immunogens or vaccines for other addictive drugs.

Microneedle-Assisted Percutaneous Delivery Of Naltrexone Hydrochloride In Yucatan Minipig: In Vitro-In Vivo Correlation. Milewski M, Paudel KS, Brogden NK, Ghosh P, Banks SL, Hammell DC, Stinchcomb AL. Mol Pharm. 2013 Oct 7; 10(10): 3745-3757.
Although microneedle-assisted transdermal drug delivery has been the subject of multiple scientific investigations, very few attempts have been made to quantitatively relate in vitro and in vivo permeation. The case of naltrexone hydrochloride is not an exception. In the present study, a pharmacokinetic profile obtained following a "poke and patch" microneedle application method in the Yucatan minipig is reported. The profile demonstrates a rapid achievement of maximum naltrexone hydrochloride plasma concentration followed by a relatively abrupt concentration decline. No steady state was achieved in vivo. In an attempt to correlate the present in vivo findings with formerly published in vitro steady-state permeation data, a diffusion-compartmental mathematical model was developed. The model incorporates two parallel permeation pathways, barrier-thickness-dependent diffusional resistance, microchannel closure kinetics, and a pharmacokinetic module. The regression analysis of the pharmacokinetic data demonstrated good agreement with an independently calculated microchannel closure rate and in vitro permeation data. Interestingly, full-thickness rather than split-thickness skin employed in in vitro diffusion experiments provided the best correlation with the in vivo data. Data analysis carried out with the model presented herein provides new mechanistic insight and permits predictions with respect to pharmacokinetics coupled with altered microchannel closure rates.

Transdermal Delivery Of Cannabidiol Attenuates Binge Alcohol-Induced Neurodegeneration In A Rodent Model Of An Alcohol Use Disorder. Liput DJ, Hammell DC, Stinchcomb AL, Nixon K. Pharmacol Biochem Behav. 2013 Oct; 111: 120-127.
Excessive alcohol consumption, characteristic of alcohol use disorders, results in neurodegeneration and behavioral and cognitive impairments that are hypothesized to contribute to the chronic and relapsing nature of alcoholism. Therefore, the current study aimed to advance the preclinical development of transdermal delivery of cannabidiol (CBD) for the treatment of alcohol-induced neurodegeneration. In Experiment 1, 1.0%, 2.5% and 5.0% CBD gels were evaluated for neuroprotection. The 5.0% CBD gel resulted in a 48.8% reduction in neurodegeneration in the entorhinal cortex assessed by Fluoro-Jade B (FJB), which trended to statistical significance ($p=0.069$). Treatment with the 5.0% CBD gel resulted in day 3 CBD plasma concentrations of ~100.0 ng/mL so this level was used as a target concentration for development of an optimized gel formulation. Experiment 2 tested a next generation 2.5% CBD gel formulation, which was compared to CBD administration by intraperitoneal injection (IP; 40.0 mg/kg/day). This experiment found similar magnitudes of neuroprotection following both routes of administration; transdermal CBD decreased FJB+ cells in the entorhinal cortex by 56.1% ($p<0.05$), while IP CBD resulted in a 50.6% ($p<0.05$) reduction in FJB+ cells. These results demonstrate the feasibility of using CBD transdermal delivery systems for the treatment of alcohol-induced neurodegeneration.

Diclofenac Enables Unprecedented Week-Long Microneedle-Enhanced Delivery Of A Skin Impermeable Medication In Humans. Brogden NK, Banks SL, Crofford LJ, Stinchcomb AL. Pharm Res. 2013 Aug; 30(8): 1947-1955.
Microneedles applied to the skin create micropores, allowing transdermal drug delivery of skin-impermeable compounds. The first human study with this technique demonstrated delivery of naltrexone (an opioid antagonist) for two to three days. Rapid micropore closure, however, blunts the delivery window. Application of diclofenac (an anti-inflammatory) allows seven days of naltrexone delivery in animals. The purpose of the current work was to demonstrate delivery of naltrexone for seven days following one microneedle treatment in humans. Human subjects were treated with microneedles, diclofenac (or placebo), and naltrexone. Impedance measurements were used as a surrogate marker to measure micropore formation, and plasma naltrexone concentrations were measured for seven days post-microneedle application. Impedance dropped significantly from baseline to post-microneedle treatment, confirming micropore formation. Naltrexone was detected for seven days in Group 1 (diclofenac + naltrexone, n=6), vs. 72 h in Group 2 (placebo + naltrexone, n=2). At study completion, a significant difference in impedance was observed between intact and microneedle-treated skin in Group 1 (confirming the presence of micropores). This is the first study demonstrating week-long drug delivery after one microneedle application, which would increase patient compliance and allow delivery of therapies for chronic diseases.

Effect Of Formulation Ph On Transport Of Naltrexone Species and Pore Closure In Microneedle-Enhanced Transdermal Drug Delivery. Ghosh P, Brogden NK, Stinchcomb AL. Mol Pharm. 2013 Jun 3; 10(6): 2331-2339.
Microneedle-enhanced transdermal drug delivery greatly improves the subset of pharmacologically active molecules that can be transported across the skin. Formulation pH plays an important role in all drug delivery systems; however, for transdermal delivery it becomes specifically significant since a wide range of pH values can be exploited for patch formulation as long as it does not lead to skin irritation or sensitization issues. Wound healing literature has shown significant pH effects on barrier recovery. Stability and solubility of the drug, and thus transport across skin, are all affected by formulation pH. The current study examined the role of ionization state of the drug naltrexone on transdermal flux and permeability across microneedle treated skin, as compared to intact skin. Impedance spectroscopy was done in pigs in vivo to assess the role of formulation pH on the rate of micropore closure under the influence of three different pH conditions. The data indicated that while there was significant advantage of using a lower pH formulation in terms of total transport across microneedle treated skin, the pH however did not have any significant effect on the rate of micropore closure beyond the first 24 h.

Reducing Cannabinoid Abuse and Preventing Relapse By Enhancing Endogenous Brain Levels Of Kynurenic Acid. Justinova Z, Mascia P, Wu HQ, Secci ME, Redhi GH, Panlilio LV, Scherma M, Barnes C, Parashos A, Zara T, Fratta W, Solinas M, Pistis M, Bergman J, Kangas BD, Ferré S, Tanda G, Schwarcz R, Goldberg SR. Nat Neurosci. 2013 Nov; 16(11): 1652-1661.
In the reward circuitry of the brain, α-7-nicotinic acetylcholine receptors (α7nAChRs) modulate effects of Δ(9)-tetrahydrocannabinol (THC), marijuana's main psychoactive ingredient. Kynurenic acid (KYNA) is an endogenous negative allosteric modulator of α7nAChRs. Here the authors report that the kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 increases

brain KYNA levels and attenuates cannabinoid-induced increases in extracellular dopamine in reward-related brain areas. In the self-administration model of drug abuse, Ro 61-8048 reduced the rewarding effects of THC and the synthetic cannabinoid WIN 55,212-2 in squirrel monkeys and rats, respectively, and it also prevented relapse to drug-seeking induced by reexposure to cannabinoids or cannabinoid-associated cues. The effects of enhancing endogenous KYNA levels with Ro 61-8048 were prevented by positive allosteric modulators of α7nAChRs. Despite a clear need, there are no medications approved for treatment of marijuana dependence. Modulation of KYNA offers a pharmacological strategy for achieving abstinence from marijuana and preventing relapse.

The Serotonin-2 Receptor Modulator, (-)-Trans-PAT, Decreases Voluntary Ethanol Consumption In Rats. Kasper J, Tikamdas R, Kim MS, Macfadyen K, Aramini R, Ladd J, Bisceglia S, Booth R, Peris J. Eur J Pharmacol. 2013 Oct 15; 718(1-3): 98-104.
Serotonin (5-HT) 5-HT2C receptor agonists have shown promise as novel alcoholism pharmacotherapies, but developing selective agonists has been problematic. Female Sprague Dawley rats were given ethanol in a palatable gel vehicle during operant sessions. 5-HT2C receptor modulators (Ro60-0175, SB242,084, and (-)-trans-PAT) were administered before operant sessions. As a control for the effects of 5-HT2C receptor agonism on caloric intake, drugs were also tested using non-ethanol containing gelatin. Ro60-0175, a 5-HT2 family receptor agonist, decreased both ethanol and vehicle responding while (-)-trans-PAT, a 5-HT2C receptor agonist with 5-HT2A-2B receptor inverse agonist activity, selectively reduced only ethanol responding. The effect of 5-HT2C receptor agonists on self-administration after reinstatement of ethanol after a three week deprivation was also determined. (-)-trans-PAT eliminated increases in ethanol intake following ethanol deprivation whereas Ro60-0175 had no effect. These results emphasize the need for caloric controls and further support the idea that selective modulation of 5-HT2 family receptors is a potential pharmacotherapeutic approach in the treatment of alcoholism.

Reduction Of Cocaine Self-Administration and D3 Receptor-Mediated Behavior By Two Novel Dopamine D3 Receptor-Selective Partial Agonists, OS-3-106 and WW-III-55. Cheung TH, Loriaux AL, Weber SM, Chandler KN, Lenz JD, Schaan RF, Mach RH, Luedtke RR, Neisewander JL. J Pharmacol Exp Ther. 2013 Nov; 347(2): 410-423.
Dopamine D3 receptor (D3R)-selective compounds may be useful medications for cocaine dependence. In this study, the authors identified two novel arylamide phenylpiperazines, OS-3-106 and WW-III-55, as partial agonists at the D3R in the adenylyl cyclase inhibition assay. OS-3-106 and WW-III-55 have 115- and 862-fold D3R:D2 receptor (D2R) binding selectivity, respectively. They investigated their effects (0, 3, 5.6, or 10 mg/kg) on operant responding by using a multiple variable-interval (VI) 60-second schedule that alternated components with sucrose reinforcement and components with intravenous cocaine reinforcement (0.375 mg/kg). Additionally, the authors evaluated the effect of OS-3-106 (10 mg/kg) on the dose-response function of cocaine self-administration and the effect of WW-III-55 (0-5.6 mg/kg) on a progressive ratio schedule with either cocaine or sucrose reinforcement. Both compounds were also examined for effects on locomotion and yawning induced by a D3R agonist. OS-3-106 decreased cocaine and sucrose reinforcement rates, increased latency to first response for cocaine but not sucrose, and downshifted the cocaine self-administration dose-response function. WW-III-55 did not affect cocaine self-administration on the multiple-variable interval schedule, but it

reduced cocaine and sucrose intake on the progressive ratio schedule. Both compounds reduced locomotion at doses that reduced responding, and both compounds attenuated yawning induced by low doses of 7-OH-DPAT (a D3R-mediated behavior), but neither affected yawning on the descending limb of the 7-OH-DPAT dose-response function (a D2R-mediated behavior). Therefore, both compounds blocked a D3R-mediated behavior. However, OS-3-106 was more effective in reducing cocaine self-administration. These findings support D3Rs, and possibly D2Rs, as targets for medications aimed at reducing the motivation to seek cocaine.

Differentiation Between Low- and High-Efficacy CB1 Receptor Agonists Using A Drug Discrimination Protocol For Rats. Järbe TU, Lemay BJ, Halikhedkar A, Wood J, Vadivel SK, Zvonok A, Makriyannis A. Psychopharmacology (Berl). 2013 Sep 5.

The "subjective high" from marijuana ingestion is likely due to Δ^9-tetrahydrocannabinol (THC) activating the central cannabinoid receptor type 1 (CB_1R) of the endocannabinoid signaling system. THC is a weak partial agonist according to in vitro assays, yet THC mimics the behavioral effects induced by more efficacious cannabinergics. This distinction may be important for understanding similarities and differences in the dose-effect spectra produced by marijuana/THC and designer cannabimimetics ("synthetic marijuana"). The authors evaluated if drug discrimination is able to functionally detect/differentiate between a full, high-efficacy CB_1R agonist [(±)AM5983] and the low-efficacy agonist THC in vivo. Rats were trained to discriminate between four different doses of AM5983 (0.10 to 0.56 mg/kg), and vehicle and dose generalization curves were determined for both ligands at all four training doses of AM5983. The high-efficacy WIN55,212-2 and the lower-efficacy (R)-(+)-methanandamide were examined at some AM5983 training conditions. Antagonism tests involved rimonabant and WIN55,212-2 and AM5983. The separate (S)- and (R)-isomers of (±)AM5983 were tested at one AM5983 training dose (0.30 mg/kg). The in vitro cyclic adenosine monophosphate (cAMP) assay examined AM5983 and the known CB_1R agonist CP55,940. Dose generalization ed_{50} values increased as a function of the training dose of AM5983, but more so for the partial agonists. The order of potency was (R)-isomer > (±)AM5983 > (S)-isomer and AM5983 > WIN55,212-2 ≥ THC > (R)-(+)-methanandamide. Surmountable antagonism of AM5983 and WIN55,212-2 occurred with rimonabant. The cAMP assay confirmed the cannabinergic nature of AM5983 and CP55,940. Drug discrimination using different training doses of a high-efficacy, full CB_1R agonist differentiated between low- and high-efficacy CB_1R agonists.

Fundamental Reaction Pathway and Free Energy Profile For Butyrylcholinesterase-Catalyzed Hydrolysis Of Heroin. Qiao Y, Han K, Zhan CG. Biochemistry. 2013 Sep 17; 52(37): 6467-6479.

The pharmacological function of heroin requires an activation process that transforms heroin into 6-monoacetylmorphine (6-MAM), which is the most active form. The primary enzyme responsible for this activation process in human plasma is butyrylcholinesterase (BChE). The detailed reaction pathway of the activation process via BChE-catalyzed hydrolysis has been explored computationally, for the first time, in this study via molecular dynamics simulation and first-principles quantum mechanical/molecular mechanical free energy calculations. It has been demonstrated that the whole reaction process includes acylation and deacylation stages. The acylation consists of two reaction steps, i.e., the nucleophilic attack on the carbonyl carbon of the 3-acetyl group of heroin by the hydroxyl oxygen of the Ser198 side chain and the dissociation of 6-MAM. The deacylation also consists of two reaction steps, i.e., the nucleophilic attack on the

carbonyl carbon of the acyl-enzyme intermediate by a water molecule and the dissociation of the acetic acid from Ser198. The calculated free energy profile reveals that the second transition state (TS2) should be rate-determining. The structural analysis reveals that the oxyanion hole of BChE plays an important role in the stabilization of rate-determining TS2. The free energy barrier (15.9 ± 0.2 or 16.1 ± 0.2 kcal/mol) calculated for the rate-determining step is in good agreement with the experimentally derived activation free energy (~16.2 kcal/mol), suggesting that the mechanistic insights obtained from this computational study are reliable. The obtained structural and mechanistic insights could be valuable for use in the future rational design of a novel therapeutic treatment of heroin abuse.

Effects of Phendimetrazine Treatment on Cocaine vs Food Choice and Extended-Access Cocaine Consumption in Rhesus Monkeys. Banks ML, Blough BE, Fennell TR, Snyder RW, Negus SS. Neuropsychopharmacology. 2013 Dec; 38(13): 2698-2707.
There is currently no Food and Drug Administration-approved pharmacotherapy for cocaine addiction. Monoamine releasers such as d-amphetamine constitute one class of candidate medications, but clinical use and acceptance are hindered by their own high-abuse liability. Phendimetrazine (PDM) is a schedule III anorectic agent that functions as both a low-potency monoamine-uptake inhibitor and as a prodrug for the monoamine-releaser phenmetrazine (PM), and it may serve as a clinically available, effective, and safer alternative to d-amphetamine. This study determined efficacy of chronic PDM to reduce cocaine self-administration by rhesus monkeys (N=4) using a novel procedure that featured both daily assessments of cocaine vs food choice (to assess medication efficacy to reallocate behavior away from cocaine choice and toward choice of an alternative reinforcer) and 20h/day cocaine access (to allow high-cocaine intake). Continuous 21-day treatment with ramping PDM doses (days 1-7: 0.32mg/kg/h; days 8-21: 1.0mg/kg/h) reduced cocaine choices, increased food choices, and nearly eliminated extended-access cocaine self-administration without affecting body weight. There was a trend for plasma PDM and PM levels to correlate with efficacy to decrease cocaine choice such that the monkey with the highest plasma PDM and PM levels also demonstrated the greatest reductions in cocaine choice. These results support further consideration of PDM as a candidate anti-cocaine addiction pharmacotherapy. Moreover, PDM may represent a novel pharmacotherapeutic approach for cocaine addiction because it may simultaneously function as both a monoamine-uptake inhibitor (via the parent drug PDM) and as a monoamine releaser (via the active metabolite PM).

Substituted 1-Phenyl-3-(Pyridin-2-Yl)Urea Negative Allosteric Modulators Of mGlu5: Discovery Of A New Tool Compound VU0463841 With Activity In Rat Models Of Cocaine Addiction. Amato RJ, Felts AS, Rodriguez AL, Venable DF, Morrison RD, Byers FW, Daniels JS, Niswender CM, Conn PJ, Lindsley CW, Jones CK, Emmitte KA. ACS Chem Neurosci. 2013 Aug 21; 4(8): 1217-1228.
Cocaine is a powerful and highly addictive stimulant that disrupts the normal reward circuitry in the central nervous system (CNS), producing euphoric effects. Cocaine use can lead to acute and life threatening emergencies, and abuse is associated with increased risk for contracting infectious diseases. Though certain types of behavioral therapy have proven effective for treatment of cocaine addiction, relapse remains high, and there are currently no approved medications for the treatment of cocaine abuse. Evidence has continued to accumulate that indicates a critical role for the metabotropic glutamate receptor subtype 5 (mGlu5) in the

modulation of neural circuitry associated with the addictive properties of cocaine. While the small molecule mGlu5 negative allosteric modulator (NAM) field is relatively advanced, investigation into the potential of small molecule mGlu5 NAMs for the treatment of cocaine addiction remains an area of high interest. Herein the authors describe the discovery and characterization of a potent and selective compound 29 (VU0463841) with good CNS exposure in rats. The utility of 29 (VU0463841) was demonstrated by its ability to attenuate drug seeking behaviors in relevant rat models of cocaine addiction.

Support For 5-HT2C Receptor Functional Selectivity In Vivo Utilizing Structurally Diverse, Selective 5-HT2C Receptor Ligands and the 2,5-Dimethoxy-4-Iodoamphetamine Elicited Head-Twitch Response Model. Canal CE, Booth RG, Morgan D. Neuropharmacology. 2013 Jul; 70: 112-121.

There are seemingly conflicting data in the literature regarding the role of serotonin (5-HT) 5-HT2C receptors in the mouse head-twitch response (HTR) elicited by the hallucinogenic 5-HT2A/2B/2C receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI). Namely, both 5-HT2C receptor agonists and antagonists, regarding 5-HT2C receptor-mediated Gq-phospholipase C (PLC) signaling, reportedly attenuate the HTR response. The present experiments tested the hypothesis that both classes of 5-HT2C receptor compounds could attenuate the DOI-elicited-HTR in a single strain of mice, C57Bl/6J. The expected results were considered in accordance with ligand functional selectivity. Commercially-available 5-HT2C agonists (CP 809101, Ro 60-0175, WAY 161503, mCPP, and 1-methylpsilocin), novel 4-phenyl-2-N,N-dimethyl-aminotetralin (PAT)-type 5-HT2C agonists (with 5-HT2A/2B antagonist activity), and antagonists selective for 5-HT2A (M100907), 5-HT2C (SB-242084), and 5-HT2B/2C (SB-206553) receptors attenuated the DOI-elicited-HTR. In contrast, there were differential effects on locomotion across classes of compounds. The 5-HT2C agonists and M100907 decreased locomotion, SB-242084 increased locomotion, SB-206553 resulted in dose-dependent biphasic effects on locomotion, and the PATs did not alter locomotion. In vitro molecular pharmacology studies showed that 5-HT2C agonists potent for attenuating the DOI-elicited-HTR also reduced the efficacy of DOI to activate mouse 5-HT2C receptor-mediated PLC signaling in HEK cells. Although there were differences in affinities of a few compounds at mouse compared to human 5-HT2A or 5-HT2C receptors, all compounds tested retained their selectivity for either receptor, regardless of receptor species. Results indicate that 5-HT2C receptor agonists and antagonists attenuate the DOI-elicited-HTR in C57Bl/6J mice, and suggest that structurally diverse 5-HT2C ligands result in different 5-HT2C receptor signaling outcomes compared to DOI.

Buprenorphine Implants For Treatment Of Opioid Dependence: Randomized Comparison To Placebo and Sublingual Buprenorphine/Naloxone. Rosenthal RN, Ling W, Casadonte P, Vocci F, Bailey GL, Kampman K, Patkar A, Chavoustie S, Blasey C, Sigmon S, Beebe KL. Addiction. 2013 Dec; 108(12): 2141-2149. Epub 2013 Sep 18.

The aim of the present study was to evaluate the safety and efficacy of buprenorphine implants (BI) versus placebo implants (PI) for the treatment of opioid dependence. A secondary aim compared BI to open-label sublingual buprenorphine/naloxone tablets (BNX). This was a randomized, double-blind, placebo-controlled trial. Subjects received either four buprenorphine implants (80mg/implant) (n=114), four placebo implants (n=54) or open-label BNX (12-16mg/day) (n=119). The study setting comprised 20 addiction treatment centers. Participants were adult out-patients (ages 18-65) with DSM-IV-TR opioid dependence. The primary efficacy

end-point was the percentage of urine samples negative for opioids collected from weeks 1 to 24, examined as a cumulative distribution function (CDF). The BI CDF was significantly different from placebo (P<0.0001). Mean [95% confidence interval (CI)] proportions of urines negative for opioids were: BI=31.2% (25.3, 37.1) and PI=13.4% (8.3, 18.6). BI subjects had a higher study completion rate relative to placebo (64 versus 26%, P<0.0001), lower clinician-rated (P<0.0001) and patient-rated (P<0.0001) withdrawal, lower patient-ratings of craving (P<0.0001) and better subjects' (P=0.031) and clinicians' (P=0.022) global ratings of improvement. BI also resulted in significantly lower cocaine use (P=0.0016). Minor implant-site reactions were comparable in the buprenorphine [27.2% (31 of 114)] and placebo groups [25.9% (14 of 54)]. BI were non-inferior to BNX on percentage of urines negative for opioids [mean (95% CI)=33.5 (27.3, 39.6); 95% CI for the difference of proportions=(-10.7, 6.2)]. Compared with placebo, buprenorphine implants result in significantly less frequent opioid use and are non-inferior to sublingual buprenorphine/naloxone tablets.

Randomized, Placebo-Controlled Pilot Trial Of Gabapentin During An Outpatient, Buprenorphine-Assisted Detoxification Procedure. Sanders NC, Mancino MJ, Gentry WB, Guise JB, Bickel WK, Thostenson J, Oliveto AH. Exp Clin Psychopharmacol. 2013 Aug; 21(4): 294-302. Epub 2013 Jul 15.

This pilot study examined the efficacy of the N-type calcium channel blocker gabapentin to improve outcomes during a brief detoxification protocol with buprenorphine. Treatment-seeking opioid-dependent individuals were enrolled in a 5-week, double-blind, placebo-controlled trial examining the effects of gabapentin during a 10-day outpatient detoxification from buprenorphine. Participants were inducted onto buprenorphine sublingual tablets during Week 1, were randomized and inducted onto gabapentin or placebo during Week 2, underwent a 10-day buprenorphine taper during Weeks 3 and 4, and then were tapered off gabapentin/placebo during Week 5. Assessments included thrice-weekly opioid withdrawal scales, vitals, and urine drug screens. Twenty-four individuals (13 male; 17 Caucasian, 3 African American, 4 Latino; mean age 29.7 years) participated in the detoxification portion of the study (gabapentin, n = 11; placebo, n = 13). Baseline characteristics did not differ significantly between groups. Self-reported and observer-rated opioid withdrawal ratings were relatively low and did not differ between groups during the buprenorphine taper. Urine results showed a Drug × Time interaction, such that the probability of opioid-positive urines significantly decreased over time in the gabapentin versus placebo groups during Weeks 3 and 4 (OR = 0.73, p = .004). These results suggest that gabapentin reduces opioid use during a 10-day buprenorphine detoxification procedure.

Preliminary Findings Of the Effects Of Rivastigmine, An Acetylcholinesterase Inhibitor, On Neurocognition In Cocaine-Dependent Volunteers. Mahoney JJ 3rd, Kalechstein AD, Verrico CD, Arnoudse NM, Shapiro BA, De La Garza R 2nd. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Nov 12. [Epub ahead of print].

Long-term cocaine use is a risk factor for the onset of neurocognitive impairment. This study sought to determine whether the acetylcholinesterase inhibitor rivastigmine (3 or 6mg) could improve neurocognitive performance in cocaine-dependent individuals. 43 cocaine-dependent individuals who were not seeking treatment at the time of enrollment in the study were randomly assigned to receive placebo (n=15), rivastigmine 3mg (n=14), or rivastigmine 6mg (n=14). The baseline neurocognitive assessment, which included measures of attention/information

processing (as measured by the Continuous Performance Task), verbal learning/episodic memory (as measured by the Hopkins Verbal Learning Test), and working memory (as measured by the Dual N-Back Task), was conducted prior to the administration of study medication (Day 0). The follow-up assessment was conducted on Day 8 after participants had received rivastigmine or placebo for seven days (Days 2-8). Rivastigmine administration significantly improved performance on one measure of working memory span (mean n-back span) and improved performance on a verbal learning/episodic memory task (HVLT total recall). This study provides additional data showing that cocaine-associated neurocognitive impairment can be remediated. Additionally, while this confirms that working memory impairments are amenable to treatment, this is to the authors' knowledge, the first study to show that cocaine-associated episodic memory impairment can be treated with cognition enhancing medications.

Topiramate For the Treatment Of Cocaine Addiction: A Randomized Clinical Trial.
Johnson BA, Ait-Daoud N, Wang XQ, Penberthy JK, Javors MA, Seneviratne C, Liu L. JAMA Psychiatry. 2013 Oct 16. doi: 10.1001/jamapsychiatry.2013.2295. [Epub ahead of print].
No medication has been established as an efficacious treatment for cocaine dependence. The authors hypothesized that dual modulation of the mesocorticolimbic dopamine system by topiramate-a glutamate receptor antagonist and γ-aminobutyric acid receptor agonist-would result in efficacious treatment for cocaine dependence compared with placebo. The objective of this study was to determine the efficacy of topiramate vs placebo as a treatment for cocaine dependence. This was a double-blind, randomized, placebo-controlled, 12-week trial of 142 cocaine-dependent adults in clinical research facilities at the University of Virginia between November 22, 2005, and July 25, 2011. Topiramate (n=71) or placebo (n=71) in escalating doses from 50 mg/d to the target maintenance dose of 300 mg/d in weeks 6 to 12, were combined with weekly cognitive-behavioral treatment. For the efficacy period, weeks 6 to 12, the primary outcome was the weekly difference from baseline in the proportion of cocaine nonuse days; the secondary outcome was urinary cocaine-free weeks, and exploratory outcomes included craving and self- and observer-rated global functioning on the Clinical Global Impression scales. Using an intent-to-treat analysis, topiramate was more efficacious than placebo at increasing the weekly proportion of cocaine nonuse days, irrespective of whether missing data were not or were imputed conservatively to the baseline value (13.3% vs 5.3%, 95% CI for the estimated mean difference, 1.4%-14.6%, P=.02 or 8.9% vs 3.7%, 95% CI for the estimated mean difference, 0.2%-10.1%, P=.04, respectively). Topiramate also was associated, significantly more than placebo, with increasing the likelihood of urinary cocaine-free weeks (16.6% vs 5.8%; odds ratio, 3.21; 95% CI, 1.24-8.32; P=.02), as well as decreasing craving and improving observer-rated global functioning (all P < .05). The authors conclude that topiramate is more efficacious than placebo at increasing the mean weekly proportion of cocaine nonuse days and associated measures of clinical improvement among cocaine-dependent individuals. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00249691.

An Adaptive Approach For Identifying Cocaine Dependent Patients Who Benefit From Extended Continuing Care. McKay JR; Van Horn DH; Lynch KG, Ivey M; Cary MS; Drapkin ML; Coviello DM; Plebani JG.. J Consult Clin Psychol 2013 Sep; [Epub ahead of print].
This study tested whether cocaine dependent patients using cocaine or alcohol at intake or in the first few weeks of intensive outpatient treatment would benefit more from extended continuing care than patients abstinent during this period. The effect of incentives for continuing care

attendance was also examined. Participants (N = 321) were randomized to treatment as usual (TAU), TAU and telephone monitoring and counseling (TMC), or TAU and TMC plus incentives (TMC+). The primary outcomes were (a) abstinence from all drugs and heavy alcohol use and (b) cocaine urine toxicology. Follow-ups were at 3, 6, 9, 12, 18, and 24 months. Cocaine and alcohol use at intake or early in treatment predicted worse outcomes on both measures (ps ≤ .0002). Significant effects favoring TMC over TAU on the abstinence composite were obtained in participants who used cocaine (odds ratio [OR] = 1.95 [1.02, 3.73]) or alcohol (OR = 2.47 [1.28, 4.78]) at intake or early in treatment. A significant effect favoring TMC+ over TAU on cocaine urine toxicology was obtained in those using cocaine during that period (OR = 0.55 [0.31, 0.95]). Conversely, there were no treatment effects in participants abstinent at baseline and no overall treatment main effects. Incentives almost doubled the number of continuing care sessions received but did not further improve outcomes. An adaptive approach for cocaine dependence in which extended continuing care is provided only to patients who are using cocaine or alcohol at intake or early in treatment improves outcomes in this group while reducing burden and costs in lower risk patients.

The Effects Of Subanesthetic Ketamine Infusions On Motivation To Quit and Cue-Induced Craving In Cocaine-Dependent Research Volunteers. Dakwar E, Levin F, Foltin RW, Nunes EV, Hart CL. Biol Psychiatry 2013 Sep; [Epub ahead of print].
Cocaine dependence involves problematic neuroadaptations that might be responsive to modulation of glutamatergic circuits. This investigation examined the effects of subanesthetic ketamine infusions on motivation for quitting cocaine and on cue-induced craving in cocaine-dependent participants, 24 hours postinfusion. Eight volunteers with active DSM-IV cocaine dependence not seeking treatment or abstinence were entered into this crossover, double-blind trial. Three 52-min intravenous infusions were administered: ketamine (.41 mg/kg or .71 mg/kg) or lorazepam 2 mg, counterbalanced into three orderings in which ketamine .41 mg/kg always preceded the .71 mg/kg dose. Infusions were separated by 48 hours, and assessments occurred at baseline and at 24 hours postinfusion. Outcomes were change between postinfusion and preinfusion values for: 1) motivation to quit cocaine scores with the University of Rhode Island Change Assessment; and 2) sums of visual analogue scale craving ratings administered during cue exposure. Compared with the active control lorazepam, a single ketamine infusion (.41 mg/kg) led to a mean 3.9-point gain in University of Rhode Island Change Assessment (p = .012), which corresponds to an approximately 60% increase over preceding values. There was a reduction of comparable magnitude in cue-induced craving (p = .012). A subsequent ketamine infusion (.71 mg/kg) led to further reductions in cue-induced craving compared with the control. Infusions were well-tolerated. Subanesthetic ketamine demonstrated promising effects on motivation to quit cocaine and on cue-induced craving, 24 hours postinfusion. Research is needed to expand on these preliminary results and to evaluate the efficacy of this intervention in clinical settings.

The Effects Of Exogenous Progesterone On Drug Craving and Stress Arousal In Cocaine Dependence: Impact Of Gender and Cue Type. Fox HC, Sofuoglu M, Morgan PT, Tuit KL, Sinha R. Psychoneuroendocrinology 2013 Sep; (9): 1532-1544.
Exogenous progesterone has been shown to attenuate the rewarding effects of cocaine. However, its effects on provoked drug craving, stress arousal and cognitive performance has not been systematically investigated in cocaine dependent men and women. Thus, the authors conducted a

double-blind placebo-controlled study assessing the efficacy of progesterone in reducing provoked drug craving, stress system arousal and improving cognitive performance in cocaine dependent men and women. Forty-two early abstinent treatment-seeking cocaine dependent individuals were randomly assigned to either daily doses of placebo (12M/9F) or micronized progesterone (12M/9F) (400 mg/day), for 7 days. Under experimental conditions, all subjects were exposed to three 5-min personalized guided imagery conditions (stress, cocaine cue, relaxing), one per day, consecutively in a random, counterbalanced order. Subjective craving, mood, hypothalamic-pituitary-adrenal (HPA) and cardiovascular output, and a cognitive measure of inhibitory control (Stroop Color Word Task) were assessed pre- and post imagery. Progesterone relative to placebo significantly decreased cue-induced craving and cortisol responses and increased cue-induced ACTH. In addition, women but not men receiving progesterone reported lower ratings of negative emotion and higher ratings of relaxed mood following stress exposure. Improved Stroop performance was observed in all participants receiving progesterone, across all conditions. Progesterone was selectively effective in reducing cocaine cue-induced but not stress-related cocaine craving as well as specific measures of the provoked arousal state. Findings suggest that progesterone's effects on drug craving and arousal are moderated by both the type of environmental cue exposure and gender.

Assessment Of Safety, Cardiovascular and Subjective Effects After Intravenous Cocaine and Lofexidine. De La Garza R 2nd, Galloway GP, Newton TF, Mendelson J, Haile CN, Dib E, Hawkins RY, Chen CY, Mahoney JJ 3rd, Mojsiak J, Lao G, Anderson A, Kahn R. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Dec 3. [Epub ahead of print].
The primary objective of this study was to determine the safety of lofexidine, an α2 receptor agonist, alone and concurrent with cocaine in non-treatment seeking cocaine-dependent or cocaine-abusing participants. After screening, eligible participants received double-blind, randomized infusions of saline and 20mg of cocaine on Day 1, and saline and 40mg of cocaine on Day 2. Subjects were randomized and started receiving daily administration of placebo (N=4) or lofexidine on Day 3 and continued on this schedule until Day 7. Two dosing regimens for lofexedine were investigated: 0.8 QID (N=3) and 0.2mg QID (N=11). On Days 6 and 7, subjects received double-blind infusions of saline and 20mg of cocaine on Day 6, and saline and 40mg of cocaine on Day 7. The data reveal a notable incidence of hemodynamic-related AEs over the course of the study. Two of the three participants at the 0.8mg dose level discontinued, and five of 11 participants at the 0.2mg dose level were withdrawn (or voluntarily discontinued) after hemodynamic AEs. Subjective effects and cardiovascular data were derived from all participants who were eligible to receive infusions (i.e., did not meet stopping criteria) on Days 6 and 7 (6 received lofexidine 0.2mg, QID and 4 received placebo, QID). As expected, cocaine significantly increased heart rate and blood pressure, as well as several positive subjective effects. There was a trend for lofexidine to decrease cocaine-induced cardiovascular changes and cocaine-induced ratings for "Any Drug Effect", "Good Effects", and "Desire Cocaine", but sample size issues limit the conclusions that can be drawn. Despite the trends to reduce cocaine-induced subjective effects, cardiovascular AEs may limit future utility of lofexidine as a treatment for this population.

Acute Effects Of Mecamylamine and Varenicline On Cognitive Performance In Non-Smokers With and Without Schizophrenia. Roh S, Hoeppner SS**,** Schoenfeld D, Fullerton CA, Stoeckel LE, Evins AE. Psychopharmacology (Berl) 2013 Oct; [Epub ahead of print].
Nicotinic acetylcholine receptors (nAChRs) have been implicated in the pathophysiology of cognitive deficits in the domains of attention and memory in schizophrenia. While nicotinic agonists and antagonists have been proposed as smoking cessation aids, few comparisons have been made of these agents on cognitive performance in individuals with schizophrenia. This study investigated the acute effects of a nAChR antagonist, mecamylamine, and partial agonist, varenicline, on cognitive function in non-smokers with and without schizophrenia. Single oral doses of mecamylamine 10 mg, varenicline 1 mg, and placebo were administered 1 week apart in random order to adults with schizophrenia (n=30) and to healthy volunteers (n=41) in a double-blind, crossover design. The primary outcome of interest was sustained attention as assessed with hit reaction time variability (HRT-SD) on the identical pairs continuous performance test (CPT-IP). Mecamylamine worsened performance on CPT-IP HRT-SD, a measure of attention, compared to varenicline in both groups. Performance on mecamylamine was worse than performance on both placebo and varenicline on several additional measures of attention, including CPT-IP hit reaction time (HRT) and random errors at various levels of task difficulty. There was a treatment by diagnosis interaction, such that mecamylamine worsened performance on CPT-IP 2-digit HRT, 3-digit random errors, and 4-digit hit rate compared to placebo and varenicline in participants with schizophrenia; effects not observed in controls.These findings support a role for nAChRs in attention and suggest that those with schizophrenia may be particularly sensitive to nAChR blockade.

Role Of Insular Cortex D1 and D2 Dopamine Receptors In Nicotine Self-Administration In Rats. Kutlu MG, Burke D; Slade, S, Hall BJ, Rose JE, Levin ED. Behav Brain Res 2013 Nov; [Epub ahead of print] 273-278.
The insular cortex has been associated with the processing of rewarding stimuli and with the neural bases of drug addiction. Ischemic damage to the insula has been associated with decreased desire to smoke cigarettes. Which component of insular function is involved in the neural basis of cigarette smoking is not clear. Dopamine systems are crucial for the reinforcing value of addictive drugs. The DA projection from the ventral tegmental area to the nucleus accumbens (NAc) has been shown to be a vital pathway for the primary reinforcement caused by taking a variety of abused drugs. In the current set of studies, the roles of D1 and D2 receptors in the insular cortex in the self-administration of nicotine by rats were assessed. Adult female Sprague-Dawley rats were fitted with jugular catheters and given access to self-administer nicotine. Bilateral local infusion cannulae were implanted into the agranular insular cortex to locally administer D1 and D2 antagonists (SCH-23390 and haloperidol). Acute local infusions of the D1 antagonist SCH-23390 into the insula (1-2μg/side) significantly decreased nicotine self-administration by more than 50%. Repeated infusions of SCH-23390 into the agranular insula caused continuing decreases in nicotine self-administration without signs of tolerance. In contrast, local infusions of the D2 antagonist haloperidol 0.5-2μg/side did not have any discernable effect on nicotine self-administration. These studies show the importance of DA D1 systems in the insula for nicotine reward.

Influence Of A Dopamine Pathway Additive Genetic Efficacy Score On Smoking Cessation: Results From Two Randomized Clinical Trials Of Bupropion. David SP, Stron DR, Leventhal AM, Lancaster MA, McGeary JE, Munafò MR, Bergen AW, Swan GE, Benowitz NL, Tyndale RF, Conti DV, Brown RA, Lerman C, Niaura R.. Addiction 2013 Dec; (12): 2202-2211.

The objective of this study was to evaluate the associations of treatment and an additive genetic efficacy score (AGES) based on dopamine functional polymorphisms with time to first smoking lapse and point prevalence abstinence at end of treatment among participants enrolled into two randomized clinical trials of smoking cessation therapies. These were double-blind pharmacogenetic efficacy trials randomizing participants to active or placebo bupropion. Study 1 also randomized participants to cognitive-behavioral smoking cessation treatment (CBT) or this treatment with CBT for depression. Study 2 provided standardized behavioural support. Study settings were two hospital-affiliated clinics (study 1), and two university-affiliated clinics (study 2). Participants were a total of 792 self-identified white treatment-seeking smokers aged ≥18 years smoking ≥10 cigarettes per day over the last year. Measures collected were age, gender, Fagerström Test for Nicotine Dependence, dopamine pathway genotypes (rs1800497 [ANKK1 E713K], rs4680 [COMT V158M], DRD4 exon 3 variable number of tandem repeats polymorphism [DRD4 VNTR], SLC6A3,3' VNTR) analyzed both separately and as part of an AGES, time to first lapse and point prevalence abstinence at end of treatment. Significant associations of the AGES (hazard ratio [HR]=1.10, 95% confidence interval [CI]=1.06-1.14, P=0.009) and of the DRD4 VNTR (HR=1.29, 95% CI=1.17-1.41, P=0.0073) were observed with time to first lapse. A significant AGES by pharmacotherapy interaction was observed (β standard error=-0.18 [0.07], P=0.016), such that AGES predicted risk for time to first lapse only for individuals randomized to placebo. A score based on functional polymorphisms relating to dopamine pathways appears to predict lapse to smoking following a quit attempt, and the association is mitigated in smokers using bupropion.

Gradual and Immediate Nicotine Reduction Result In Similar Low-Dose Nicotine Self-Administration. Smith TT, Levin ME, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Gradual and immediate nicotine reduction result in similar low-dose nicotine self-administration. Nicotine Tob Res 2013 Nov; (11): 1918-1925.

Food and Drug Administration-mandated product standards that drastically reduce nicotine content in cigarettes aim to decrease smoking and thus improve health outcomes for millions of U.S. smokers. Researchers have suggested that nicotine reduction should be implemented gradually, but a gradual nicotine reduction may shift the minimum level of nicotine required to reinforce behavior or may result in different levels of compensatory smoking behavior. Rats were given the opportunity to acquire nicotine self-administration at 60 µg/kg/infusion nicotine with a cocktail of other tobacco constituents included as the vehicle. Rats were subsequently assigned to one of six immediate dose reductions (30, 15, 7.5, 3.75, 1.875, or 0.0 µg/kg/infusion) for 10 sessions (n = 9-15). Rats in the 30 µg/kg/infusion reduction group continued to have their nicotine dose reduced by half after at least 10 sessions at each dose until reaching 1.875 µg/kg/infusion (i.e., gradual reduction). For both methods of reduction, reduction to 3.75 µg/kg/infusion resulted in significant decreases in behavior. Reduction to doses above 3.75 µg/kg/infusion resulted in only limited compensation. The largest compensation was temporary. There was no compensation following reduction to 3.75 µg/kg/infusion or below. This study suggests that reduction to the same nicotine dose will result in similar reductions in behavior for

both gradual and immediate reductions, and both methods result in similar compensation. Future studies using humans should investigate differences in other outcomes such as withdrawal and craving.

Apoe ε4, An Alzheimers Disease Susceptibility Allele, and Smoking Cessation. Ashare RL, Karlawish JH, Wileyto EP, Pinto A, Lerman C. Pharmacogenomics J 2013 Dec; (6): 538-543. Possessing an apolipoprotein E (APOE) ε4 allele, advanced age and smoking are risk factors for Alzheimer's disease and cognitive decline. Deficits in cognitive function also increase risk for smoking relapse. Data from 917 adult smokers of European ancestry were pooled across three randomized trials of smoking cessation. The authors examined whether smokers who carry at least one ε4 allele (n=252) have more difficulty quitting smoking compared with noncarriers (n=665), and whether age moderated this association. The genotype by age interaction was significant for 7-day point-prevalence abstinence rates (P=0.04) and time to 7-day failure (P=0.03). Among smokers over age 60, ε4 carriers were less likely to quit (odds ratio=0.27, P=0.018) and relapsed more quickly (hazard ratio=3.38, P=0.001) compared with noncarriers. The genotype association with relapse was nonsignificant among younger smokers. An increased understanding of the underlying pathophysiological mechanisms of this association could facilitate the development of targeted therapies for smokers with increased risk for cognitive decline.

Gabapentin Treatment For Alcohol Dependence: A Randomized Clinical Trial. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. JAMA Intern Med 2013 Nov, [Epub ahead of print].
Approved medications for alcohol dependence are prescribed for less than 9% of US alcoholics. The objective of this study was to determine if gabapentin, a widely prescribed generic calcium channel/γ-aminobutyric acid-modulating medication, increases rates of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia dysphoria and craving in a dose-dependent manner. This was a 12-week double-blind placebo-controlled randomized dose-ranging trial of 150 men and women older than 18 years with current alcohol dependence conducted from 2004 through 2010 at a single-site outpatient clinical research facility adjoining a general medical hospital. Interventions were oral gabapentin (dosages of 0 [placebo] 900 mg or 1800 mg/d) and concomitant manual-guided counseling. Main outcomes and measures obtained were rates of complete abstinence and no heavy drinking (coprimary) and changes in mood sleep and craving (secondary) over the 12-week study. Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI 1.1%-13.7%) in the placebo group 11.1% (95% CI 5.2%-22.2%) in the 900-mg group and 17.0% (95% CI 8.9%-30.1%) in the 1800-mg group (P=.04 for linear dose effect, number needed to treat [NNT]=8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI 13.6%-37.2%) in the placebo group 29.6% (95% CI 19.1%-42.8%) in the 900-mg group and 44.7% (95% CI 31.4%-58.8%) in the 1800-mg group (P=.02 for linear dose effect, NNT=5 for 1800 mg). Similar linear dose effects were obtained with measures of mood (F2=7.37, P=.001) sleep (F2=136, P=.001) and craving (F2=3.56, P=.03). There were no serious drug-related adverse events and terminations owing to adverse events (9 of 150 participants) time in the study (mean [SD] 9.1 [3.8] weeks) and rate of study completion (85 of 150 participants) did not differ among groups. Gabapentin (particularly the 1800-mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia dysphoria and craving with a favorable safety profile. Increased implementation of

pharmacological treatment of alcohol dependence in primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00391716.

Differential Effects Of Acute and Chronic Treatment With The A2-Adrenergic Agonist, Lofexidine, On Cocaine Self-Administration In Rhesus Monkeys. Kohut SJ, Fivel PA, Mello NK. Drug Alcohol Depend. 2013 Dec 1; 133(2): 593-599.
Lofexidine, an α2-adrenergic agonist, is being investigated as a treatment for reducing opioid withdrawal symptoms and blocking stress-induced relapse to cocaine taking. Opioid abusers are often polydrug abusers and cocaine is one frequent drug of choice. However, relatively little is known about lofexidine interactions with cocaine. The present study investigated the effects of acute and chronic treatment with lofexidine in a pre-clinical model of cocaine self-administration. Male rhesus monkeys were trained to respond for food (1g) and cocaine (0.01mg/kg/injection) under a fixed ratio 30 (FR30) or a second order FR2 (VR16:S) schedule of reinforcement. Systematic observations of behavior were conducted during and after chronic treatment with lofexidine. Acute treatment with lofexidine (0.1 or 0.32mg/kg, IM) significantly reduced cocaine self-administration but responding for food was less effected. In contrast, chronic treatment (7-10days) with lofexidine (0.1-0.32mg/kg/h, IV) produced a leftward shift in the cocaine self-administration dose-effect curve, but had no effect on food-maintained responding. Lofexidine did not produce any observable side effects during or after treatment. Lofexidine potentiated cocaine's reinforcing effects during chronic treatment. These data suggest that it is unlikely to be effective as a cocaine abuse medication and could enhance risk for cocaine abuse in polydrug abusers.

Effects Of Methcathinone and 3-Cl-Methcathinone (Pal-434) In Cocaine Discrimination Or Self-Administration In Rhesus Monkeys. Kohut SJ, Fivel PA, Blough BE, Rothman RB, Mello NK. Int J Neuropsychopharmacol. 2013 Oct; 16(9): 1985-1998.
Monoamine releasers with varying selectivity for dopamine (DA)/norepinephrine and serotonin (5-HT) release are potential treatment medications for cocaine abuse. Although DA-selective monoamine releasers effectively reduce cocaine abuse, their clinical usefulness is limited by abuse liability. It is hypothesized that increasing 5-HT neurotransmission may reduce the abuse-related effects of DA releasers, but the optimal DA:5-HT release ratio remains to be determined. This study in rhesus monkeys compared the effects of two compounds with differing potency for 5-HT release. Methcathinone and 3-Cl-methcathinone (PAL-434) have equal potency for DA release, but PAL-434 has 10-fold higher potency for 5-HT release. In drug discrimination studies, monkeys were trained to discriminate cocaine (0.4 mg/kg i.m.) from saline in a two-key, food-reinforced procedure. In drug self-administration studies, a separate group of monkeys was trained to respond for cocaine [0.01 mg/kg/injection (inj)] and food (1 g pellets) under a second order schedule of reinforcement [FR2(VR16:S)]. When responding was stable, methcathinone (0.1–0.56 mg/kg.h i.v.) or PAL-434 (0.32–1.8 mg/kg.h i.v.) was administered chronically (one injection every 20 min for 23 h/d) for 7–10 d. In discrimination studies, both compounds dose-dependently increased cocaine-like responding but with different potencies (cocaine=methcathinone >PAL-434). Chronic treatment with methcathinone or PAL-434 dose-dependently and selectively reduced cocaine self-administration. PAL-434 was about 4-fold and methcathinone about 1.6-fold more potent at decreasing cocaine- over food-maintained

responding. These data suggest that compounds with moderate selectivity for DA vs. 5-HT release (8–15-fold) may be effective for the treatment of cocaine dependence.

Nicotine Levels After IV Nicotine and Cigarette Smoking In Men. Mello NK, Peltier MR, Duncanson H. Exp Clin Psychopharmacol. 2013 Jun;21 (3): 188-195.
There has been considerable interest in the pharmacodynamics and pharmacokinetics of nicotine and the influence of different routes of administration. However, these variables are often examined in separate studies, and there is less information about the temporal relation between subjective reports and plasma nicotine levels. This study examined the time course and magnitude of plasma nicotine levels and reports of subjective "high" in nicotine-dependent men after 12 or more hrs of abstinence. The effects of two doses of IV nicotine and two doses of nicotine from cigarette smoking were compared, and samples were collected at 2-min intervals. Plasma nicotine levels after smoking a high-nicotine cigarette were significantly greater than after either dose of IV nicotine ($p < .001$). However, Visual Analog Scale (VAS) ratings of "high" after both doses of IV nicotine and smoking a high-nicotine cigarette did not differ significantly, and followed a similar time course. After smoking a low-nicotine cigarette, VAS ratings of "high" were significantly lower than after either IV nicotine dose or smoking a high-nicotine cigarette ($p < .001$). Peak levels of "high" were reported within 2 min after IV nicotine administration and the onset of cigarette smoking. Then "high" ratings abruptly decreased, while plasma nicotine rose to peak levels within 4 to 6 min after IV nicotine and 12 to 14 min during cigarette smoking. Plasma nicotine levels did not appear to determine the magnitude or time course of subjective effects under these conditions

Effects Of Repeated Treatment With the Dopamine D2/D3 Receptor Partial Agonist Aripiprazole On Striatal D2/D3 Receptor Availability In Monkeys. Czoty PW, Gage HD, Garg PK, Garg S, Nader MA. Psychopharmacology (Berl). 2013 Sep 29. [Epub ahead of print].
Chronic treatment with dopamine (DA) receptor agonists and antagonists can differentially affect measures of DA D2/D3 receptor number and function, but the effects of chronic treatment with a partial D2/D3 receptor agonist are not clear. The author used a within-subjects design in male cynomolgus monkeys to determine the effects of repeated (17-day) treatment with the D2/D3 receptor partial agonist aripiprazole (ARI; 0.03 mg/kg and 0.1 mg/kg i.m.) on food-reinforced behavior (n=5) and on D2/D3 receptor availability as measured with positron emission tomography (PET; n=9). Five monkeys responded under a fixed-ratio 50 schedule of food reinforcement and D2/D3 receptor availability was measured before and 4 days after ARI treatment using PET and the D2/D3 receptor-selective radioligand [^{18}F]fluoroclebopride (FCP). Four additional monkeys were studied using [^{11}C]raclopride and treated sequentially with each dose of ARI for 17 days. ARI decreased food-maintained responding with minimal evidence of tolerance. Repeated ARI administration increased FCP and raclopride distribution volume ratios (DVRs) in the caudate nucleus and putamen in most monkeys, but decreases were observed in monkeys with the highest baseline DVRs. The results indicate that repeated treatment with a low-efficacy DA receptor partial agonist produces effects on brain D2/D3 receptor availability that are qualitatively different from those of both high-efficacy receptor agonists and antagonists, and suggest that the observed individual differences in response to ARI treatment may reflect its partial agonist activity.

The Relative Reinforcing Strength Of Methamphetamine and D-Amphetamine In Monkeys Self-Administering Cocaine. Lile JA, Charnigo RJ, Nader MA. Behav Pharmacol. 2013 Sep; 24(5-6): 482-485.
Epidemiological data indicate that rates of methamphetamine misuse surpass those of D-amphetamine, but self-administration research in animals and humans has not typically demonstrated differences in their reinforcing effects. The present study used a within-session, exponentially increasing progressive-ratio schedule and extended-access conditions to assess the relative reinforcing strength of D-amphetamine and methamphetamine in rhesus monkeys (n=5) trained to self-administer cocaine. A range of doses of methamphetamine (0.003-0.1 mg/kg/injection), D-amphetamine (0.003-0.1 mg/kg/injection), and cocaine (0.003-0.3 mg/kg/injection) was tested to capture the ascending and descending limbs of the dose-effect functions. Each drug functioned as a reinforcer, but the peak number of self-administered D-amphetamine injections was significantly lower compared with methamphetamine and cocaine; the peak number of self-administered injections of cocaine and methamphetamine did not differ. Although differences in availability and other social factors likely impact relative rates of abuse, the present data suggest that the greater reinforcing strength of methamphetamine contributes to its increased use compared with D-amphetamine.

Effects Of Chronic Methylphenidate In Adolescence On Later Methylphenidate Self-Administration In Rhesus Monkeys. Martelle SE, Porrino LJ, Nader MA. Behav Pharmacol. 2013 Sep; 24(5-6): 478-481.
Many children diagnosed with attention deficit hyperactivity disorder are treated with methylphenidate (MPH), despite limited information on later vulnerability to drug abuse. A previous study in adolescent monkeys treated with MPH for 1 year did not indicate differences in acquisition to cocaine reinforcement compared with controls. The present study extended this characterization to include MPH self-administration. Adolescent male rhesus monkeys treated previously with a sustained-release formulation of MPH (beginning at ~30 months old) and control monkeys (n=8/group) were used. All had previous experience of self-administering cocaine under a fixed-ratio 30 schedule of reinforcement. Responding was maintained by food (1.0-g banana-flavored pellets) and MPH (saline, 0.001-0.1 mg/kg/injection) was substituted for food for at least five consecutive sessions. MPH functioned as a reinforcer in all monkeys; there were no differences between groups in MPH self-administration. These findings extend earlier research with cocaine reinforcement showing that MPH treatment in adolescent monkeys does not increase future reinforcing effects of stimulant drugs.

Abuse-Related and Abuse-Limiting Effects Of Methcathinone and the Synthetic "Bath Salts" Cathinone Analogs Methylenedioxypyrovalerone (MDPV), Methylone and Mephedrone On Intracranial Self-Stimulation In Rats. Bonano JS, Glennon RA, De Felice LJ, Banks ML, Negus SS. Psychopharmacology (Berl). 2013 Aug 15. [Epub ahead of print].
Abuse of synthetic cathinones, popularized as "bath salts," has increased dramatically in the USA since their debut in 2010. Preclinical behavioral studies may clarify determinants of the abuse-related effects produced by these compounds. This study examined behavioral effects of (±)-methcathinone, (±)-3,4-methylenedioxypyrovalerone (MDPV), (±)-3,4-methylenedioxy-methcathinone (methylone), and (±)-4-methylmethcathinone (mephedrone) in rats using intracranial self-stimulation (ICSS). Male Sprague-Dawley rats (n=18) with electrodes targeting the medial forebrain bundle responded for multiple frequencies of brain stimulation and were

tested in two phases. First, dose-effect curves for methcathinone (0.1-1.0 mg/kg), MDPV (0.32-3.2 mg/kg), methylone (1.0-10 mg/kg), and mephedrone (1.0-10 mg/kg) were determined. Second, time courses were determined for effects produced by the highest dose of each compound. Methcathinone produced dose- and time-dependent facilitation of ICSS. MDPV, methylone, and mephedrone produced dose- and time-dependent increases in low rates of ICSS maintained by low brain stimulation frequencies, but also produced abuse-limiting depression of high ICSS rates maintained by high brain stimulation frequencies. Efficacies to facilitate ICSS were methcathinone ≥ MDPV ≥ methylone > mephedrone. Methcathinone was the most potent compound, and MDPV was the longest acting compound. All compounds facilitated ICSS at some doses and pretreatment times, which is consistent with abuse liability for each of these compounds. However, efficacies of compounds to facilitate ICSS varied, with methcathinone displaying the highest efficacy and mephedrone displaying the lowest efficacy to facilitate ICSS.

Acute and Chronic Effects of The M1/M 4-Preferring Muscarinic Agonist Xanomeline On Cocaine Vs. Food Choice In Rats. Thomsen M, Fulton BS, Caine SB. Psychopharmacology (Berl). 2013 Aug 31. [Epub ahead of print].
The authors previously showed that the M_1/M_4-preferring muscarinic agonist xanomeline can acutely attenuate or eliminate cocaine self-administration in mice. Medications used to treat addictions will arguably be administered in (sub)chronic or repeated regimens. Tests of acute effects often fail to predict chronic effects, highlighting the need for chronic testing of candidate medications. Rats were trained to lever press under a concurrent FR5 FR5 schedule of intravenous cocaine and food reinforcement. Once baseline behavior stabilized, the effects of 7 days once-daily injections of xanomeline were evaluated. Xanomeline pretreatment dose-dependently (1.8-10 mg/kg/day) shifted the dose-effect curve for cocaine rightward (up to 5.6-fold increase in A_{50}), with reallocation of behavior to the food-reinforced lever. There was no indication of tolerance, rather effects grew over days. The suppression of cocaine choice appeared surmountable at high cocaine doses, and xanomeline treatment did not significantly decrease total-session cocaine or food intake. In terms of xanomeline's potential for promoting abstinence from cocaine in humans, the findings were mixed. Xanomeline did produce reallocation of behavior from cocaine to food with a robust increase in food reinforcers earned at some cocaine/xanomeline dose combinations. However, effects appeared surmountable, and food-maintained behavior was also decreased at some xanomeline/cocaine dose combinations, suggesting clinical usefulness may be limited. These data nevertheless support the notion that chronic muscarinic receptor stimulation can reduce cocaine self-administration. Future studies should show whether ligands with higher selectivity for M_1 or M_1/M_4 subtypes would be less limited by undesired effects and can achieve higher efficacy.

Sex Differences In Nicotine Self-Administration In Rats During Progressive Unit Dose Reduction: Implications For Nicotine Regulation Policy. Grebenstein P, Burroughs D, Zhang Y, Lesage MG. Pharmacol Biochem Behav. 2013 Nov 4; 114-115C:70-81.
Reducing the nicotine content in tobacco products is being considered by the FDA as a policy to reduce the addictiveness of tobacco products. Understanding individual differences in response to nicotine reduction will be critical to developing safe and effective policy. Animal and human research demonstrating sex differences in the reinforcing effects of nicotine suggests that males and females may respond differently to nicotine-reduction policies. However, no studies have directly examined sex differences in the effects of nicotine unit-dose reduction on nicotine self-

administration (NSA) in animals. The purpose of the present study was to examine this issue in a rodent self-administration model. Male and female rats were trained to self-administer nicotine (0.06mg/kg) under an FR 3 schedule during daily 23h sessions. Rats were then exposed to saline extinction and reacquisition of NSA, followed by weekly reductions in the unit dose (0.03 to 0.00025mg/kg) until extinction levels of responding were achieved. Males and females were compared with respect to baseline levels of intake, resistance to extinction, degree of compensatory increases in responding during dose reduction, and the threshold reinforcing unit dose of nicotine. Exponential demand-curve analysis was also conducted to compare the sensitivity of males and females to increases in the unit price (FR/unit dose) of nicotine (i.e., elasticity of demand or reinforcing efficacy). Females exhibited significantly higher baseline intake and less compensation than males. However, there were no sex differences in the reinforcement threshold or elasticity of demand. Dose-response relationships were very well described by the exponential demand function (r^2 values>0.96 for individual subjects). These findings suggest that females may exhibit less compensatory smoking in response to nicotine reduction policies, even though their nicotine reinforcement threshold and elasticity of demand may not differ from males.

Oral Administration Of GZ-793A, A VMAT2 Inhibitor, Decreases Methamphetamine Self-Administration In Rats. Wilmouth CE, Zheng G, Crooks PA, Dwoskin LP, Bardo MT. Pharmacol Biochem Behav. 2013 Nov; 112: 29-33.
Despite the high prevalence of use of methamphetamine (METH), there is no FDA-approved pharmacological treatment available currently for METH addiction. The vesicular monoamine transporter (VMAT2) has been proposed as a novel target to treat METH abuse. GZ-793A, a lobelane analog and selective VMAT2 inhibitor, has been shown previously to decrease METH self-administration specifically when administered via the subcutaneous route in rats. Since oral administration is the preferred clinical route, the present experiments determined if oral administration of GZ-793A would decrease specifically METH self-administration. Experiments 1 and 2 assessed the dose-effect functions of oral administration of GZ-793A (30-240mg/kg) on intravenous METH self-administration and food-maintained responding, respectively. Experiments 3 and 4 assessed the time-course (20-180min pretreatment) of oral administration of GZ-793A on METH self-administration and food-maintained responding, respectively. Oral administration of GZ-793A dose-dependently decreased METH self-administration, with the highest dose (240mg/kg) producing an 85% decrease compared to control baseline. The decrease in METH self-administration produced by GZ-793A (120mg/kg) lasted at least 180min. In contrast, GZ-793A failed to alter food-maintained responding at any of the doses or pretreatment intervals tested. The oral effectiveness and the specificity of GZ-793A to decrease methamphetamine self-administration support the feasibility of developing VMAT2 inhibitors as treatments for METH abuse.

Synthesis and Evaluation Of Novel Azetidine Analogs As Potent Inhibitors Of Vesicular [3H]Dopamine Uptake. Ding D, Nickell JR, Deaciuc AG, Penthala NR, Dwoskin LP, Crooks . Bioorg Med Chem. 2013 Nov 1; 21(21): 6771-6777.
Lobelane analogs that incorporate a PA central piperidine or pyrrolidine moiety have previously been reported by our group as potent inhibitors of VMAT2 function. Further central ring size reduction of the piperidine moiety in lobelane to a four-membered heterocyclic ring has been carried out in the current study to afford novel cis-and trans-azetidine analogs. These azetidine

analogs (15a-15c and 22a-22c) potently inhibited [(3)H]dopamine (DA) uptake into isolated synaptic vesicles (Ki⩽66nM). The cis-4-methoxy analog 22b was the most potent inhibitor (Ki=24nM), and was twofold more potent that either lobelane (2a, Ki=45nM) or norlobelane (2b, Ki=43nM). The trans-methylenedioxy analog, 15c (Ki=31nM), was equipotent with the cis-analog, 22b, in this assay. Thus, cis- and trans-azetidine analogs 22b and 15c represent potential leads in the discovery of new clinical candidates for the treatment of methamphetamine abuse.

Effects Of VMAT2 Inhibitors Lobeline and GZ-793A On Methamphetamine-Induced Changes In Dopamine Release, Metabolism and Synthesis In Vivo. Meyer AC, Neugebauer NM, Zheng G, Crooks PA, Dwoskin LP, Bardo MT. J Neurochem. 2013 Oct; 127(2): 187-198. Vesicular monoamine transporter-2 (VMAT2) inhibitors reduce methamphetamine (METH) reward in rats. The current study determined the effects of VMAT2 inhibitors lobeline (LOB; 1 or 3 mg/kg) and N-(1,2R-dihydroxylpropyl)-2,6-cis-di(4-methoxyphenethyl)piperidine hydrochloride (GZ-793A; 15 or 30 mg/kg) on METH-induced (0.5 mg/kg, SC) changes in extracellular dopamine (DA) and its metabolite dihydroxyphenylacetic acid (DOPAC) in the reward-relevant nucleus accumbens (NAc) shell using in vivo microdialysis. The effect of GZ-793A (15 mg/kg) on DA synthesis in tissue also was investigated in NAc, striatum, medial prefrontal cortex and orbitofrontal cortex. In NAc shell, METH produced a time-dependent increase in extracellular DA and decrease in DOPAC. Neither LOB nor GZ-793A alone altered extracellular DA; however, both drugs increased extracellular DOPAC. In combination with METH, LOB did not alter the effects of METH on DA; however, GZ-793A, which has greater selectivity than LOB for inhibiting VMAT2, reduced the duration of the METH-induced increase in extracellular DA. Both LOB and GZ-793A enhanced the duration of the METH-induced decrease in extracellular DOPAC. METH also increased tissue DA synthesis in NAc and striatum, whereas GZ-793A decreased synthesis; no effect of METH or GZ-793A on DA synthesis was found in medial prefrontal cortex or orbitofrontal cortex. These results suggest that selective inhibition of VMAT2 produces a time-dependent decrease in DA release in NAc shell as a result of alterations in tyrosine hydroxylase activity, which may play a role in the ability of GZ-793A to decrease METH reward.

GZ-793A, A Lobelane Analog, Interacts With the Vesicular Monoamine Transporter-2 To Inhibit the Effect Of Methamphetamine. Horton DB, Nickell JR, Zheng G, Crooks PA, Dwoskin LP. J Neurochem. 2013 Oct; 127(2): 177-186. (R)-3-[2,6-cis-Di(4-methoxyphenethyl)piperidin-1-yl]propane-1,2-diol (GZ-793A) inhibits methamphetamine-evoked dopamine release from striatal slices and methamphetamine self-administration in rats. GZ-793A potently and selectively inhibits dopamine uptake at the vesicular monoamine transporter-2 (VMAT2). This study determined GZ-793A's ability to evoke [^{3}H]dopamine release and inhibit methamphetamine-evoked [^{3}H]dopamine release from isolated striatal synaptic vesicles. Results show GZ-793A concentration-dependent [^{3}H]dopamine release; nonlinear regression revealed a two-site model of interaction with VMAT2 (High- and Low-EC_{50} = 15.5 nM and 29.3 μM, respectively). Tetrabenazine and reserpine completely inhibited GZ-793A-evoked [^{3}H]dopamine release, however, only at the High-affinity site. Low concentrations of GZ-793A that interact with the extravesicular dopamine uptake site and the High-affinity intravesicular DA release site also inhibited methamphetamine-evoked [^{3}H]dopamine release from synaptic vesicles. A rightward shift in the methamphetamine concentration-response was evident with increasing concentrations of GZ-793A, and the Schild

regression slope was 0.49 ± 0.08, consistent with surmountable allosteric inhibition. These results support a hypothetical model of GZ-793A interaction at more than one site on the VMAT2 protein, which explains its potent inhibition of dopamine uptake, dopamine release via a High-affinity tetrabenazine- and reserpine-sensitive site, dopamine release via a Low-affinity tetrabenazine- and reserpine-insensitive site, and a low-affinity interaction with the dihydrotetrabenazine binding site on VMAT2. GZ-793A inhibition of the effects of methamphetamine supports its potential as a therapeutic agent for the treatment of methamphetamine abuse.

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

Directly Administered Antiretroviral Therapy For HIV-Infected Individuals In Opioid Treatment Programs: Results From A Randomized Clinical Trial. Lucas GM, Mullen BA, Galai N, Moore RD, Cook K, McCaul ME, Glass S, Oursler KK, Rand C. PLoS One. 2013 Jul 16;8(7):e68286. doi: 10.1371/journal.pone.0068286. Print 2013.

Data regarding the efficacy of directly administered antiretroviral therapy (DAART) are mixed. Opioid treatment programs (OTPs) provide a convenient framework for DAART. In a randomized controlled trial, the authors compared DAART and self-administered therapy (SAT) among HIV-infected subjects attending five OTPs in Baltimore, MD. HIV-infected individuals attending OTPs were eligible if they were not taking antiretroviral therapy (ART) or were virologically failing ART at last clinical assessment. In subjects assigned to DAART, the authors observed one ART dose per weekday at the OTP for up to 12 months. SAT subjects administered ART at home. The primary efficacy comparison was the between-arm difference in the average proportions with HIV RNA <50 copies/mL during the intervention phase (3-, 6-, and 12-month study visits), using a logistic regression model accounting for intra-person correlation due to repeated observations. Adherence was measured with electronic monitors in both arms. The authors randomized 55 and 52 subjects from five Baltimore OTPs to DAART and SAT, respectively. The average proportions with HIV RNA <50 copies/mL during the intervention phase were 0.51 in DAART and 0.40 in SAT (difference 0.11, 95% CI: -0.020 to 0.24). There were no significant differences between arms in electronically-measured adherence, average CD4 cell increase from baseline, average change in log10 HIV RNA from baseline, opportunistic conditions, hospitalizations, mortality, or the development of new drug resistance mutations. In this randomized trial, the authors found little evidence that DAART provided clinical benefits compared to SAT among HIV-infected subjects attending OTPs.

Hepatitis C Viremia and the Risk of Chronic Kidney Disease in HIV-Infected Individuals. Lucas GM, Jing Y, Sulkowski M, Abraham AG, Estrella MM, Atta MG, Fine DM, Klein MB, Silverberg MJ, Gill MJ, Moore RD, Gebo KA, Sterling TR, Butt AA, for the NA-ACCORD of the IeDEA J Infect Dis. 2013 Oct 15;208(8):1240-9. doi: 10.1093/infdis/jit373. Epub 2013 Jul 31.

The role of active hepatitis C virus (HCV) replication in chronic kidney disease (CKD) risk has not been clarified. The authors compared CKD incidence in a large cohort of HIV-infected subjects who were HCV seronegative, HCV viremic (detectable HCV RNA), or HCV aviremic (HCV seropositive, undetectable HCV RNA). Stages 3 and 5 CKD were defined according to standard criteria. Progressive CKD was defined as a sustained 25% glomerular filtration rate (GFR) decrease from baseline to a GFR < 60 mL/min/1.73 m2. The authors used Cox models to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). A total of 52,602 HCV seronegative, 9508 HCV viremic, and 913 HCV aviremic subjects were included. Compared with HCV seronegative subjects, HCV viremic subjects were at increased risk for stage 3 CKD (adjusted HR 1.36 [95% CI, 1.26, 1.46]), stage 5 CKD (1.95 [1.64, 2.31]), and progressive CKD (1.31 [1.19, 1.44]), while HCV aviremic subjects were also at increased risk for stage 3 CKD (1.19 [0.98, 1.45]), stage 5 CKD (1.69 [1.07, 2.65]), and progressive CKD (1.31 [1.02, 1.68]). The authors conclude that compared with HIV-infected subjects who were HCV seronegative, both HCV viremic and HCV aviremic individuals were at increased risk for

moderate and advanced CKD.

Dual-Mixed HIV-1 Coreceptor Tropism and HIV-Associated Neurocognitive Deficits. Morris SR, Woods SP, Deutsch R, Little SJ, Wagner G, Morgan EE, Heaton RK, Letendre SL, Grant I, Smith DM. J Neurovirol. 2013 Oct; 19(5): 488-494.
HIV coreceptor usage of CXCR4 (X4) is associated with decreased CD4+ T-cell counts and accelerated disease progression, but the role of X4 tropism in HIV-associated neurocognitive disorders (HAND) has not previously been described. This longitudinal study evaluated data on 197 visits from 72 recently HIV-infected persons who had undergone up to four sequential neurocognitive assessments over a median of 160 days (IQR, 138–192). Phenotypic tropism testing (Trofile ES, Monogram, Biosciences) was performed on stored blood samples. Multivariable mixed model repeated measures regression was used to determine the association between HAND and dual-mixed (DM) viral tropism, estimated duration of infection (EDI), HIV RNA, CD4 count, and problematic methamphetamine use. Six subjects (8.3 %) had DM at their first neurocognitive assessment and four converted to DM in subsequent sampling (for total of 10 DM) at a median EDI of 10.1 months (IQR, 7.2–12.2). There were 44 (61.1 %) subjects who demonstrated HAND on at least one study visit. HAND was associated with DM tropism (odds ratio, 4.4; 95 % CI, 0.9–20.5) and shorter EDI (odds ratio 1.1 per month earlier; 95 % CI, 1.0–1.2). This study found that recency of HIV-1 infection and the development of DM tropism may be associated with HAND in the relatively early stage of infection. Together, these data suggest that viral interaction with cellular receptors may play an important role in the early manifestation of HAND.

Integration Of Health Services Improves Multiple Healthcare Outcomes Among HIV-Infected People Who Inject Drugs In Ukraine. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. Drug Alcohol Depend. 2014 Jan 1;134C:106-114. doi: 10.1016/j.drugalcdep.2013.09.020. Epub 2013 Sep 27.
People who inject drugs (PWID) experience poor outcomes and fuel HIV epidemics in middle-income countries in Eastern Europe and Central Asia. The authors assess integrated/co-located (ICL) healthcare for HIV-infected PWID, which despite international recommendations, is neither widely available nor empirically examined. This was a 2010 cross-sectional study of randomly sampled 296 HIV-infected opioid-dependent PWID from two representative HIV-endemic regions in Ukraine where ICL, non-co-located (NCL) and harm reduction/outreach (HRO) settings are available. ICL settings provide onsite HIV, addiction, and tuberculosis services, NCLs only treat addiction, and HROs provide counseling, needles/syringes, and referrals, but no opioid substitution therapy (OST). The primary outcome was receipt of quality healthcare, measured using a quality healthcare indicator (QHI) composite score representing percentage of eight guidelines-based recommended indicators met for HIV, addiction and tuberculosis treatment. The secondary outcomes were individual QHIs and health-related quality-of-life (HRQoL). On average, ICL-participants had significantly higher QHI composite scores compared to NCL- and HRO-participants (71.9% versus 54.8% versus 37.0%, $p<0.001$) even after controlling for potential confounders. Compared to NCL-participants, ICL-participants were significantly more likely to receive antiretroviral therapy (49.5% versus 19.2%, $p<0.001$), especially if CD4≤200 (93.8% versus 62.5% $p<0.05$); guideline-recommended OST dosage (57.3% versus 41.4%, $p<0.05$); and isoniazid preventive therapy (42.3% versus 11.2%, $p<0.001$). Subjects receiving OST had significantly higher HRQoL than those not receiving it

($p<0.001$); however, HRQoL did not differ significantly between ICL- and NCL-participants. These findings suggest that OST alone improves quality-of-life, while receiving care in integrated settings collectively and individually improves healthcare quality indicators for PWID.

Correlates of Elevated Interleukin-6 and C-Reactive Protein in Persons With or at High Risk for HCV and HIV Infections. Salter ML, Lau B, Mehta SH, Go VF, Leng S, Kirk GD. J Acquir Immune Defic Syndr. 2013 Dec 15;64(5):488-95. doi: 10.1097/QAI.0b013 e3182a7ee2e. HIV and hepatitis C virus (HCV) infections may increase interleukin-6 (IL-6) and C-reactive protein (CRP). However, relationships between inflammatory biomarkers, chronic viral infections, clinical factors, and behavioral factors remain poorly understood. Using linear regression, the authors modeled cross-sectional associations between loge IL-6 or loge CRP levels and HCV, HIV, injection drug use, and comorbidity among 1191 injection drug users. Mean age was 47 years, 46.0% reported currently injecting drugs, 59.0% were HCV monoinfected, and 27% were HCV/HIV coinfected. In multivariable models, higher loge IL-6 was associated with HCV monoinfection [$\beta = 0.191$, 95% confidence interval (CI): 0.043 to 0.339] and HCV/HIV coinfection ($\beta = 0.394$, 95% CI: 0.214 to 0.574). In contrast, HCV monoinfection ($\beta = -0.523$, 95% CI: -0.275 to -0.789) and HCV/HIV coinfection ($\beta = -0.554$ 95% CI: -0.260 to -0.847) were associated with lower CRP. Lower CRP with HCV infection was independent of liver fibrosis severity, synthetic function, or liver injury markers; CRP decreased with higher HCV RNA. Increased injection intensity was associated with higher IL-6 ($P = 0.003$) and CRP ($P < 0.001$); increasing comorbidity ($P < 0.001$) and older age ($P = 0.028$) were associated with higher IL-6; older age was associated with higher CRP among HCV-uninfected participants ($P = 0.021$). The authors conclude that HIV and HCV infections contribute to chronic inflammation; however, reduced CRP possibly occurs through HCV-mediated mechanisms. Findings highlight potentially modifiable contributors to inflammation.

Vitamin D Deficiency Is Associated With Coronary Artery Calcification In Cardiovascularly Asymptomatic African Americans With HIV Infection. Lai S, Fishman EK, Gerstenblith G, Brinker J, Tai H, Chen S, Li J, Tong W, Detrick B, Lai H. Vasc Health Risk Manag. 2013; 9: 493-500. doi: 10.2147/VHRM.S48388. Epub 2013 Aug 26.
Patients with HIV infection are at increased risk for coronary artery disease (CAD), and growing evidence suggests a possible link between vitamin D deficiency and clinical/subclinical CAD. However, the relationship between vitamin D deficiency and coronary artery calcification (CAC), a sensitive marker for subclinical CAD, in those with HIV infection is not well investigated. CAC was quantified using a Siemens Cardiac 64 scanner, and vitamin D levels and the presence of traditional and novel risk factors for CAD were obtained in 846 HIV-infected African American (AA) participants aged 25 years or older in Baltimore, MD, USA without symptoms or clinical evidence of CAD. The prevalence of vitamin D deficiency (25-hydroxy vitamin D <10 ng/mL) was 18.7%. CAC was present in 238 (28.1%) of the 846 participants. Logistic regression analysis revealed that the following factors were independently associated with CAC: age (adjusted odds ratio [OR]: 1.11; 95% confidence interval [CI]: 1.08-1.14); male sex (adjusted OR: 1.71; 95% CI: 1.18-2.49); family history of CAD (adjusted OR: 1.53; 95% CI: 1.05-2.23); total cholesterol (adjusted OR: 1.006; 95% CI: 1.002-1.010); high-density lipoprotein cholesterol (adjusted OR: 0.989; 95% CI: 0.979-0.999); years of cocaine use (adjusted OR: 1.02; 95% CI: 1.001-1.04); duration of exposure to protease inhibitors (adjusted OR: 1.004; 95% CI:

1.001-1.007); and vitamin D deficiency (adjusted OR: 1.98; 95% CI: 1.31-3.00). Both vitamin D deficiency and CAC are prevalent in AAs with HIV infection. In order to reduce the risk for CAD in HIV-infected AAs, vitamin D levels should be closely monitored. These data also suggest that clinical trials should be conducted to examine whether vitamin D supplementations reduce the risk of CAD in this AA population.

Vitamin D Deficiency Is Associated With Development Of Subclinical Coronary Artery Disease In HIV-Infected African American Cocaine Users With Low Framingham-Defined Cardiovascular Risk. Lai H, Fishman EK, Gerstenblith G, Moore R, Brinker JA, Keruly JC, Chen S, Detrick B, Lai S. Vasc Health Risk Manag. 2013; 9: 729-377. doi: 10.2147/VHRM.S50537. Epub 2013 Nov 15.
Chronic cocaine use may lead to premature atherosclerosis, but the prevalence of and risk factors for coronary artery disease (CAD) in asymptomatic cocaine users have not been reported. The objective of this study was to examine whether vitamin D deficiency is associated with the development of CAD in human immunodeficiency virus (HIV)-infected African American cocaine users with low CAD risk. In this prospective follow-up study, the authors investigated 169 HIV-infected African American cocaine users with low Framingham risk at baseline. The main outcome measures were incidence of subclinical CAD and development of subclinical CAD. Fifty of the 169 African Americans had evidence of subclinical disease on the initial cardiac computed tomography. A second cardiac computed tomography was performed on the 119 African Americans without disease on the first scan. The total sum of person-years of follow-up was 289.6. Subclinical CAD was detected in 11 of these, yielding an overall incidence of 3.80/100 person-years (95% confidence interval 1.90–6.80). Among the factors investigated, only vitamin D deficiency was independently associated with development of subclinical CAD. The study did not find significant associations between CD4 count, HIV viral load, or antiretroviral treatment use and the incidence of subclinical CAD. This study appears to suggest that there is a threshold level of vitamin D (10 ng/mL) above which the effect of vitamin D on subclinical CAD is diminished. The incidence of subclinical CAD in HIV-infected African American cocaine users with low CAD risk is high, especially in those with vitamin D deficiency. Well designed randomized clinical trials are warranted to confirm the role of vitamin D deficiency in the development of CAD in HIV-infected African American cocaine users with low CAD risk.

"I Did Not Feel Like A Mother": The Success and Remaining Challenges To Exclusive Formula Feeding Among HIV-Positive Women In Brazil. MacCarthy S, Rasanathan JJ, Nunn A, Dourado I. AIDS Care. 2013; 25(6): 726-731. doi: 10.1080/09540121.2013.793274.
Exclusive and safe formula feeding can eliminate the risk of vertical HIV transmission due to breastfeeding. Therefore, many countries advise all HIV-positive women to avoid breastfeeding their infants. However, little research explores the experiences of women attempting to exclusively formula feed in countries with free and universal access to highly active antiretroviral therapy (HAART). This article examines the success of Brazil in supporting HIV-positive women to engage in exclusive formula feeding (EFF). The authors conducted in-depth interviews with 30 HIV-positive women receiving care at the primary facility for HIV/AIDS in Salvador, Brazil about their attitudes and practices related to EFF as well as challenges with adhering to EFF. All interviews were recorded, professionally transcribed and translated, and then analyzed. Their results showed that one woman reported both breastfeeding and formula

feeding her infant; all others reported EFF. Postpartum counseling regarding the risk of HIV transmission through breastfeeding was the primary motivation for EFF. Challenges included difficulty reconciling their perceptions that breastfeeding is an important maternal responsibility, trouble accepting that breastfeeding can cause potential to harm their infants, confronting HIV-related stigma associated with EFF, and unexpected financial burdens due to EFF. The authors conclude that HIV-positive women adhered to national guidelines recommending EFF; this phenomenon has likely contributed to declining rates of vertical transmission in Brazil. Despite this success, many women experienced challenges with EFF. Greater support services may enhance Brazil's success in empowering HIV-positive women and eliminating vertical HIV transmission via breastfeeding.

Project Power: Adapting An Evidence-Based HIV/STI Prevention Intervention For Incarcerated Women. Fasula AM, Fogel CI, Gelaude D, Carry M, Gaiter J, Parker S. AIDS Educ Prev. 2013 Jun; 25(3): 203-215. doi: 10.1521/aeap.2013.25.3.203.
Incarcerated women are a critical population for targeted HIV/STI prevention programming; however, there is a dearth of evidence-based, gender specific behavioral interventions for this population. Systematically adapting existing evidence-based interventions (EBIs) can help fill this gap. The authors illustrate the adaptation of the HIV/STI prevention EBI, Project Safe, for use among incarcerated women and delivery in prisons. Project POWER, the final adapted intervention, was developed using formative research with prison staff and administration, incarcerated and previously incarcerated women, and input of community advisory boards. Intervention delivery adaptations included: shorter, more frequent intervention sessions; booster sessions prior to and just after release; facilitator experience in prisons and counseling; and new videos. Intervention content adaptations addressed issues of empowerment, substance use, gender and power inequity in relationships, interpersonal violence, mental health, reentry, and social support. This illustration of the adaption process provides information to inform additional efforts to adapt EBIs for this underserved population.

"Damaging What Wasn't Damaged Already": Psychological Tension and Antiretroviral Adherence Among HIV-Infected Methadone-Maintained Drug Users. Batchelder AW, Brisbane M, Litwin AH, Nahvi S, Berg KM, Arnsten JH. AIDS Care. 2013 Nov; 25(11): 1370-1374. doi: 10.1080/09540121.2013.766303. Epub 2013 Feb 13.
Active drug use among HIV-infected persons is associated with poor adherence to highly active antiretroviral therapy (HAART) and suboptimal treatment outcomes. To understand adherence experiences among HIV-infected drug users, the authors conducted semistructured interviews with 15 participants in a randomized controlled trial evaluating the efficacy of directly observed HAART delivered in methadone maintenance clinics. Interviews were recorded, transcribed, and thematically analyzed. The authors identified negative and positive psychological themes associated with both drug use and adherence. Participants described tension between negative feelings (denial, shame, and perceived isolation) and positive feelings (acceptance, motivation, empowerment, and perceived connectedness), and they associated this tension with their own drug using and adherence behaviors. Sustained antiretroviral therapy adherence may require increased emphasis on understanding the psychological experience of HIV-infected drug users.

Effect Of Micronutrient Supplementation On Disease Progression In Asymptomatic, Antiretroviral-Naive, HIV-Infected Adults In Botswana: A Randomized Clinical Trial. Baum MK, Campa A, Lai S, Sales Martinez S, Tsalaile L, Burns P, Farahani M, Li Y, van Widenfelt E, Page JB, Bussmann H, Fawzi WW, Moyo S, Makhema J, Thior I, Essex M, Marlink R. JAMA. 2013 Nov 27; 310(20): 2154-2163. doi: 10.1001/jama.2013.280923.
Micronutrient deficiencies occur early in human immunodeficiency virus (HIV) infection, and supplementation with micronutrients may be beneficial; however, its effectiveness has not been investigated early in HIV disease among adults who are antiretroviral therapy (ART) naive. The objective of this study was to investigate whether long-term micronutrient supplementation is effective and safe in delaying disease progression when implemented early in adults infected with HIV subtype C who are ART-naive. This was a randomized clinical trial of supplementation with either daily multivitamins (B vitamins and vitamins C and E), selenium alone, or multivitamins with selenium vs placebo in a factorial design for 24 months. The study was conducted in 878 patients infected with HIV subtype C with a CD4 cell count greater than 350/μL who were not receiving ART at Princess Marina Hospital in Gaborone, Botswana, between December 2004 and July 2009. Daily oral supplements of B vitamins and vitamins C and E, selenium alone, or multivitamins plus selenium were compared with placebo. Main outcomes and measures obtained were reaching a CD4 cell count less than 200/μL until May 2008; after this date, reaching a CD4 cell count of 250/μL or less, consistent with the standard of care in Botswana for initiation of ART at the time of the study. There were 878 participants enrolled and randomized into the study. All participants were ART-naive throughout the study. In intent-to-treat analysis, participants receiving the combined supplement of multivitamins plus selenium had a significantly lower risk vs placebo of reaching CD4 cell count 250/μL or less (adjusted hazard ratio [HR], 0.46; 95% CI, 0.25-0.85; P=.01; absolute event rate [AER], 4.79/100 person-years; censoring rate, 0.92; 17 events; placebo AER, 9.22/100 person-years; censoring rate, 0.85; 32 events). Multivitamins plus selenium in a single supplement, vs placebo, also reduced the risk of secondary events of combined outcomes for disease progression (CD4 cell count ≤250/μL, AIDS-defining conditions, or AIDS-related death, whichever occurred earlier [adjusted HR, 0.56; 95% CI, 0.33-0.95; P=.03; AER, 6.48/100 person-years; censoring rate, 0.90; 23 events]). There was no effect of supplementation on HIV viral load. Multivitamins alone and selenium supplementation alone were not statistically different from placebo for any end point. Reported adverse events were adjudicated as unlikely to be related to the intervention, and there were no notable differences in incidence of HIV-related and health-related events among study groups. In ART-naive HIV-infected adults, 24-month supplementation with a single supplement containing multivitamins and selenium was safe and significantly reduced the risk of immune decline and morbidity. Micronutrient supplementation may be effective when started in the early stages of HIV disease.

Glomerular Filtration Rate Estimated Using Creatinine, Cystatin C Or Both Markers and the Risk Of Clinical Events In HIV-Infected Individuals. Lucas G, Cozzi-Lepri A, Wyatt C, Post F, Bormann A, Crum-Cianflone N, Ross M; INSIGHT SMART Study Group. HIV Med. 2013 Sep 11. doi: 10.1111/hiv.12087. [Epub ahead of print].
The accuracy and precision of glomerular filtration rate (GFR) estimating equations based on plasma creatinine (GFR_{cr}), cystatin C (GFR_{cys}) and the combination of these markers ($GFR_{cr\text{-}cys}$) have recently been assessed in HIV-infected individuals. The authors assessed the associations of GFR, estimated by these three equations, with clinical events in HIV-infected

individuals. They compared the associations of baseline GFR_{cr} , GFR_{cys} and $GFR_{cr\text{-}cys}$ [using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations] with mortality, cardiovascular events (CVEs) and opportunistic diseases (ODs) in the Strategies for the Management of Antiretroviral Therapy (SMART) study. They used Cox proportional hazards models to estimate unadjusted and adjusted hazard ratios per standard deviation (SD) change in GFR. A total of 4614 subjects from the SMART trial with available baseline creatinine and cystatin C data were included in this analysis. Of these, 99 died, 111 had a CVE and 121 had an OD. GFR_{cys} was weakly to moderately correlated with HIV RNA, CD4 cell count, high-sensitivity C-reactive protein, interleukin-6, and D-dimer, while GFR_{cr} had little or no correlation with these factors. GFR_{cys} had the strongest associations with the three clinical outcomes, followed closely by $GFR_{cr\text{-}cys}$, with GFR_{cr} having the weakest associations with clinical outcomes. In a model adjusting for demographics, cardiovascular risk factors, HIV-related factors and inflammation markers, a 1-SD lower GFR_{cys} was associated with a 55% [95% confidence interval (CI) 27-90%] increased risk of mortality, a 21% (95% CI 0-47%) increased risk of CVE, and a 22% (95% CI 0-48%) increased risk of OD. Of the three CKD-EPI GFR equations, GFR_{cys} had the strongest associations with mortality, CVE and OD.

Comparison Of Risk Factors and Outcomes In HIV Immune Complex Kidney Disease and HIV-Associated Nephropathy. Foy MC, Estrella MM, Lucas GM, Tahir F, Fine DM, Moore RD, Atta MG. Clin J Am Soc Nephrol. 2013 Sep; 8(9): 1524-1532. doi: 10.2215/CJN.10991012. Epub 2013 May 16.
HIV-associated nephropathy (HIVAN) is well described, but the clinical features of a group of renal pathologies characterized by Ig or immune complex depositions referred to as HIV-associated immune complex kidney disease (HIVICK) have not been well established. The objective of this study is to assess risk factors for HIVICK compared with contemporaneous control participants. A nested case-control study of 751 HIV-infected patients followed from January 1996 to June 2010 was conducted. Groups were compared using the chi-squared test or rank-sum analysis. Conditional logistic regression was used to estimate odds ratios (ORs) for HIVICK. Incidences of overall ESRD and with/without combined antiretroviral therapy (cART) exposure were calculated. HIVICK patients were predominantly African American (92%). Compared with matched controls, patients with HIVICK were more likely to have HIV RNA >400 copies/ml (OR, 2.5; 95% confidence interval [95% CI], 1.2 to 5.2), diabetes (OR, 2.8; 95% CI, 1.1 to 6.8), and hypertension (OR, 2.3; 95% CI, 1.2 to 4.5). Compared with HIVAN, patients with HIVICK had more antiretroviral therapy exposure, lower HIV viral loads, and higher CD4 and estimated GFR. ESRD was less common in the HIVICK versus the HIVAN group (30% versus 82%; $P<0.001$), and the use of cART was not associated with ESRD in HIVICK patients (25% versus 26; $P=0.39$). HIVICK was predominantly observed in African-American patients and associated with advanced HIV disease. ESRD incidence is lower in HIVICK patients compared with those with HIVAN. Unlike HIVAN, cART use was not associated with the incidence of ESRD in HIVICK.

Pain Is Associated With Heroin Use Over Time In HIV-Infected Russian Drinkers. Tsui JI, Cheng DM, Coleman SM, Blokhina E, Bridden C, Krupitsky E, Samet JH. Addiction. 2013 Oct; 108(10): 1779-1787. doi: 10.1111/add.12274. Epub 2013 Jul 24.
The aims of this study were to evaluate whether pain was associated with increased risk of using heroin, stimulants or cannabis among HIV-infected drinkers in Russia. This was a secondary

analysis of longitudinal data from the HERMITAGE study (HIV's Evolution in Russia-Mitigating Infection Transmission and Alcoholism in a Growing Epidemic), a behavioral randomized controlled trial, with data collected at baseline, 6-month and 12-month visits. Recruitment occurred at HIV and addiction treatment sites in St Petersburg, Russian Federation. Six hundred and ninety-nine HIV-infected adult drinkers. The primary outcome was past month illicit drug use; secondary outcomes examined each drug (heroin, stimulants and cannabis) separately. The main predictor was pain that interfered at least moderately with daily living. General estimating equations (GEE) logistic regression models were used to evaluate the association between pain and subsequent illicit drug use, adjusting for potential confounders. Participants reporting pain appeared to have higher odds of using illicit drugs, although the results did not reach statistical significance [adjusted odds ratio (OR)= 1.32; 95% confidence interval (CI)= 0.99, 1.76, P = 0.06]. There was a significant association between pain and heroin use (OR = 1.54; 95% CI = 1.11-2.15, P = 0.01) but not use of other drugs (OR = 0.75; 95% CI =0.40-1.40, P = 0.35 for stimulants and OR = 0.70; 95% CI = 0.45-1.07, P = 0.09 for cannabis). HIV-infected Russian drinkers who report pain are more likely to use heroin over time than HIV-infected Russian drinkers who do not report pain. Pain may be an unrecognized risk factor for persistent heroin use with implications for HIV transmission in Russia.

Downregulation Of Bone Morphogenetic Protein Receptor Axis During HIV-1 and Cocaine-Mediated Pulmonary Smooth Muscle Hyperplasia: Implications For HIV-Related Pulmonary Arterial Hypertension. Dalvi P, O'Brien-Ladner A, Dhillon NK. Arterioscler Thromb Vasc Biol. 2013 Nov;33(11):2585-95. doi: 10.1161/ATVBAHA.113.302054. Epub 2013 Sep 5.

The authors' previous findings support an additive effect of cocaine to HIV infection in the development of pulmonary arteriopathy through enhanced proliferation of human pulmonary smooth muscle cells. They now examined the role of antiproliferative bone morphogenetic protein receptor (BMPR) axis in HIV protein and cocaine-mediated pulmonary smooth muscle hyperplasia. Stimulation of BMPR axis resulted in attenuation of synergistic increase in the proliferation of human pulmonary arterial smooth muscle cells in response to cocaine and HIV protein, transactivator of transcription (Tat). Interestingly, an increase in mRNA but decrease in protein levels of BMPR with correlated decrease in the activation of Sma- and MAD-related family protein 1/5/8 and Id1 gene expression was observed on combined treatment with cocaine and Tat when compared with the untreated cells at all time points tested. Although longer exposure to either cocaine or Tat alone also resulted in a significant decrease in the BMPR protein expression, the abrogation on combined treatment was still significantly more when compared with that of the monotreatments. Significant increase in mRNA but downmodulation of BMPR protein expression was also observed in the lung extracts from HIV-infected intravenous drug users (HIV+IVDU) when compared with that from HIV-infected non-IVDUs (HIV) or uninfected IVDUs (IVDU). Furthermore, significant decrease in BMPR protein expression was also observed in HIV or IVDUs when compared with normal controls that correlated with in vitro findings on chronic exposure to cocaine or HIV protein alone. Simultaneous exposure of pulmonary smooth muscle cells to viral protein(s) and cocaine exacerbates downregulation of BMPR axis that may result in enhanced pulmonary vasculature aberrations in HIV+IVDUs.

Anti-Inflammatory Cytokines, Pro-Fibrogenic Chemokines and Persistence Of Acute HCV Infection. Osburn WO, Levine JS, Chattergoon MA, Thomas DL, Cox AL. J Viral Hepat. 2013 Jun; 20(6): 404-413. doi: 10.1111/jvh.12052. Epub 2013 Feb 6.
Chemokines and cytokines play a vital role in directing and regulating immune responses to viral infections. Persistent hepatitis C virus (HCV) infection is characterized by the loss of anti-HCV cellular immune responses, while control of HCV infection is associated with maintenance of anti-HCV cellular immune responses. To determine whether plasma concentrations of 19 chemokines and cytokines controlling T-cell trafficking and function differed based on infection outcome, the authors compared them in at-risk subjects followed prospectively for HCV infection. Levels were compared over time in subjects who controlled HCV infection (Clearance) and subjects who developed persistent HCV infection (Persistence) at two time points during acute infection: (i) first viraemic sample (initial viraemia) and (ii) last viraemic sample in Clearance subjects and time-matched samples in Persistence subjects. At initial viraemia, increased pro-inflammatory tumour necrosis factor α (TNFα) plasma concentrations were observed in the Clearance group, while the plasma levels of anti-inflammatory interleukin (IL)-2, IL-10 and IL-13 were higher in the Persistence group. IL-13 was positively correlated with IL-2 and IL-10 at initial viraemia in the Persistence group. At the time of last viraemia, plasma levels of eotaxin, macrophage chemoattractant protein-4 (MCP-4), IL-5 and IL-10 were higher in the Persistence group and IL-10 and IL-5 levels were positively correlated. Collectively, these results suggest that the development of persistent infection is associated with an anti-inflammatory and pro-fibrogenic chemokine and cytokine profile that is evident at the onset of infection and maintained throughout acute infection.

Maintenance Of Th1 Hepatitis C Virus (HCV)-Specific Responses In Individuals With Acute HCV Who Achieve Sustained Virological Clearance After Treatment. Flynn JK, Dore GJ, Hellard M, Yeung B, Rawlinson WD, White PA, Kaldor JM, Lloyd AR, Ffrench RA; ATAHC Study Group. 2013 Nov;28(11):1770-81. doi: 10.1111/jgh.12265.
T-cell responses against hepatitis C are believed to be critical in achieving both natural and treatment-induced clearance. However, rapid clearance of antigen with early treatment of primary infection may result in reduced or poorly sustained cellular immunity. This study longitudinally examined Th1 and Th2 hepatitis C virus (HCV)-specific cytokine production and T-cell effector function from subjects enrolled in the Australian Trial in Acute Hepatitis C comparing three groups: treatment-induced clearance (sustained virological response [SVR]), treatment non-response, and untreated spontaneous clearance. HCV-specific T-cell responses were characterized by HCV peptide ELISpot, in vitro cytokine production, and T-cell flow cytometry assays. Treated subjects with a sustained virological response (SVR) displayed a better maintenance of HCV-specific Th1 responses compared to treatment non-responders (higher interferon [IFN]-γ and interleukin (IL)-2 magnitude at week 24, broader IFN-γ responses at weeks 24 and 48, P<.05) and significantly increased IFN-γ responses between screening and week 48 (magnitude P=0.026, breadth P=0.009). Treatment-induced viral clearance was also associated with a trend toward decreased IL-10 responses (screening to week 48, P=0.070), higher expression of CD45RO (P=0.042) and CD38 (P=0.088) on CD4+ T cells, and higher IFN-γR expression (CD56+ IFN-γR+ P=0.033) compared to treatment non-responders. Untreated subjects with viral clearance also displayed high magnitude and broad HCV-specific IFN-γ and IL-2 responses early in infection; however, IFN-γ responses were not as well maintained compared to treated subjects with a SVR (week 48 magnitude, breadth P=0.064). Treatment-

induced viral clearance of recent HCV infection is associated with maintenance of HCV-specific Th1 responses.

Diabetes Mellitus and Advanced Liver Fibrosis Are Risk Factors For Severe Anaemia During Telaprevir-Based Triple Therapy. Crismale JF, Martel-Laferrière V, Bichoupan K, Schonfeld E, Pappas A, Wyatt C, Odin JA, Liu LU, Schiano TD, Perumalswami PV, Bansal M, Dieterich DT, Branch AD. Liver Int. 2013 Oct 1. doi: 10.1111/liv.12342. [Epub ahead of print].
Adding telaprevir to pegylated-interferon and ribavirin increased both response rates and side effects of hepatitis C virus (HCV) treatment. The authors identified variables associated with severe anaemia during telaprevir-based triple therapy. An observational study was performed on 142 HCV-infected patients between June 2011 and March 2012. All subjects completed 12 weeks of telaprevir-based triple therapy or discontinued early because of anaemia. Severe anaemia was defined by a haemoglobin ≤8.9 g/dl; advanced fibrosis was determined by Fib-4 ≥3.25. The 47 (33%) patients who developed severe anaemia were similar to those who did not in sex, race, and prior response to dual therapy, but they were more likely to have diabetes (23.4% vs. 6.3%, P < 0.01), advanced fibrosis (46.8% vs. 29.5%, P = 0.04) and a history of anaemia during previous dual therapy (29.7% vs. 11.4%, P = 0.02). Patients developing severe anaemia were older (59 vs. 56 years, P = 0.02), had lower baseline platelet counts (134 vs. 163 × 10^9 /L, P = 0.04), haemoglobin (14.0 vs. 15.0 g/dl, P < 0.01), estimated glomerular filtration rate (79 vs. 90 ml/min/1.73 m^2 , P = 0.03) and a higher median ribavirin/weight ratio (14.9 vs. 13.2 mg/kg, P < 0.01). In multivariable logistic regression, presence of diabetes (OR = 5.61, 95% CI: 1.59-19.72), Fib-4 ≥3.25 (OR = 3.09, 95% CI: 1.28-7.46), higher ribavirin/weight ratio (OR = 1.31 per mg/kg, 95% CI: 1.13-1.52) and lower baseline haemoglobin (OR = 0.57 per g/dl, 95% CI, 0.41-0.80) were independently associated with developing severe anaemia. Severe anaemia occurred in one-third of patients receiving telaprevir-based triple therapy. Risk was greater in patients with diabetes, advanced liver fibrosis, higher ribavirin/weight ratio and lower baseline haemoglobin.

Virological Response Rates For Telaprevir-Based Hepatitis C Triple Therapy In Patients With and Without HIV Coinfection. Martel-Laferrière V, Brinkley S, Bichoupan K, Posner S, Stivala A, Perumalswami P, Schiano T, Sulkowski M, Dieterich D, Branch A. HIV Med. 2013 Sep 11. doi: 10.1111/hiv.12086. [Epub ahead of print].
Pegylated-interferon/ribavirin dual therapy for hepatitis C virus (HCV) infection has a lower sustained virological response (SVR) rate in HIV/HCV-coinfected patients than in HCV monoinfected patients, but little is known about the relative effectiveness of teleprevir-based triple therapy in the two groups. Data on 33 coinfected and 116 monoinfected patients were analysed on an intention-to-treat basis. SVR12 was defined as undetectable HCV RNA at week 12 post-end-of-treatment, severe anaemia as haemoglobin ≤89g/L or a drop of ≥45g/L, and advanced fibrosis/cirrhosis as Fib-4 ≥3.25. All coinfected patients had well controlled HIV infection. The groups were similar in age, gender, percentage with Fib-4 ≥3.25 and HCV viral load, but differed in previous treatment response, with more coinfected patients being nonresponders or treatment-intolerant (75.8% vs. 50.0% for monoinfected patients; P<0.01). During treatment, the percentages of patients with undetectable HCV RNA were similar, but, surprisingly, this percentage tended to be higher in coinfected patients. SVR12 rates were 60.6% in coinfected patients vs. 42.2% in monoinfected patients (P=0.06). In multivariable analysis, SVR12 was associated with HIV infection [odds ratio (OR) 3.55; P<0.01], African American

race (OR 0.37; P=0.03) and previous treatment response (OR 0.46; P=0.03). Rates of severe anaemia (45.5 vs. 58.6% in coinfected and monoinfected patients, respectively; P=0.18) were similar in the two groups, but rash (15.2 vs. 34.5%, respectively; P=0.03) and rectal symptoms (12.1 vs. 43.1%, respectively; P<0.01) were less common in coinfected patients. Virological responses of coinfected and monoinfected patients did not differ significantly, but tended to be higher in coinfected patients, who had a 60.6% SVR12 rate. Telaprevir-based triple therapy is a promising option for coinfected patients with well-controlled HIV infection.

In HIV/Hepatitis C Virus Co-Infected Patients, Higher 25-Hydroxyvitamin D Concentrations Were Not Related To Hepatitis C Virus Treatment Responses But Were Associated With Ritonavir Use. Branch AD, Kang M, Hollabaugh K, Wyatt CM, Chung RT, Glesby MJ. Am J Clin Nutr. 2013 Aug; 98(2): 423-429. doi: 10.3945/ajcn.112.048785. Epub 2013 Jun 5.

Among patients with hepatitis C virus (HCV) monoinfection, 25-hydroxyvitamin D [25(OH)D] concentrations are positively associated with a response to peg-interferon/ribavirin. Data on the relation between 25(OH)D concentrations and HCV treatment response in HIV-infected patients are limited. The objective of this study was to determine whether baseline 25(OH)D concentrations predict virologic response in HIV/HCV co-infected patients and to examine variables associated with 25(OH)D concentrations ≥30 ng/mL. Data and samples from 144 HCV genotype 1, treatment-naive patients from a completed HCV treatment trial were examined in this retrospective study. Early virologic response (EVR) was defined as ≥2 log10 reduction in HCV RNA and/or HCV RNA <600 IU/mL at week 12 of peg-interferon/ribavirin treatment. Baseline 25(OH)D was measured by liquid chromatography/tandem mass spectrometry. Compared with the non-EVR control group (n = 68), the EVR group (n = 76) was younger, had fewer cirrhotic subjects, had a higher proportion with the IL28B CC genotype, had a higher albumin concentration, and had a lower HCV viral load at baseline (P ≤ 0.05). The difference in baseline 25(OH)D concentrations between EVR and non-EVR patients was not statistically significant (median: 25 ng/mL compared with 20 ng/mL; P = 0.23). Similar results were found for sustained virologic response (SVR). In multivariable analysis, white and Hispanic race-ethnicity (OR: 6.26; 95% CI: 2.47, 15.88; P = 0.0001) and ritonavir use (OR: 2.68; 95% CI: 1.08, 6.65; P = 0.033) were associated with higher 25(OH)D concentrations (≥30 ng/mL). Baseline 25(OH)D concentrations did not predict EVR or SVR. Because ritonavir impairs the conversion of 25(OH)D to the active metabolite, utilization of 25(OH)D may have been impaired in subjects taking ritonavir. This trial was registered at www.clinicaltrials.gov as NCT00078403.

Kinetic Differences In the Induction Of Interferon Stimulated Genes By Interferon-A and IL28B Are Altered By Infection With Hepatitis C Virus. Jilg N, Lin W, Hong J, Schaefer EA, Wolski D, Meixong J, Goto K, Brisac C, Chusri P, Fusco DN, Chevaliez S, Luther J, Kumthip K, Urban TJ, Peng LF, Lauer GM, Chung RT. Hepatology. 2013 Aug 1. doi: 10.1002/hep.26653. [Epub ahead of print].

Several genome-wide association studies (GWAS) have identified a genetic polymorphism associated with the gene locus for interleukin 28B (IL28B), a type III interferon (IFN), as a major predictor of clinical outcome in hepatitis C. Antiviral effects of the type III IFN family have previously been shown against several viruses, including hepatitis C virus (HCV), and resemble the function of type I IFN including utilization of the intracellular JAK-STAT pathway. Effects unique to IL28B that would distinguish it from IFN-α are not well defined. By analyzing

the transcriptomes of primary human hepatocytes (PHH) treated with IFN-α or IL28B, the authors sought to identify functional differences between IFN-α and IL28B to better understand the roles of these cytokines in the innate immune response. Although their data did not reveal distinct gene signatures, the authors detected striking kinetic differences between IFN-α and IL28B stimulation for interferon stimulated genes (ISGs). While gene induction was rapid and peaked at 8 h of stimulation with IFN-α in PHH, IL28B produced a slower, but more sustained increase in gene expression. The authors confirmed these findings in the human hepatoma cell line Huh7.5.1. Interestingly, in HCV infected cells, the rapid response after stimulation with IFN-α was blunted, and the induction pattern resembled that caused by IL28B. In conclusion, the authors describe the kinetics of gene induction as being fundamentally different for stimulations with either IFN-α or IL28B in hepatocytes suggesting distinct roles of these cytokines within the immune response. Furthermore, they demonstrate that the observed differences are substantially altered by infection with the hepatitis C virus. (Hepatology 2013;).

Synergism of Tapasin and Human Leukocyte Antigens In Resolving Hepatitis C Virus Infection. Ashraf S, Nitschke K, Warshow UM, Brooks CR, Kim AY, Lauer GM, Hydes TJ, Cramp ME, Alexander G, Little AM, Thimme R, Neumann-Haefelin C, Khakoo SI. Hepatology. 2013 Sep; 58(3): 881-889. doi: 10.1002/hep.26415. Epub 2013 Jul 29.
CD8+ T-cell responses to hepatitis C virus (HCV) are important in generating a successful immune response and spontaneously clearing infection. Human leukocyte antigen (HLA) class I presents viral peptides to CD8+ T cells to permit detection of infected cells, and tapasin is an important component of the peptide loading complex for HLA class I. The authors sought to determine if tapasin polymorphisms affected the outcome of HCV infection. Patients with resolved or chronic HCV infection were genotyped for the known G/C coding polymorphism in exon 4 of the tapasin gene. In a European, but not a US, Caucasian population, the tapasin G allele was significantly associated with the outcome of HCV infection, being found in 82.5% of resolvers versus 71.3% of persistently infected individuals (P=0.02, odds ratio [OR]=1.90 95% confidence interval [CI]=1.11-3.23). This was more marked at the HLA-B locus at which heterozygosity of both tapasin and HLA-B was protective (P<0.03). Individuals with an HLA-B allele with an aspartate at residue 114 and the tapasin G allele were more likely to spontaneously resolve HCV infection (P<0.00003, OR=3.2 95% CI=1.6-6.6). Additionally, individuals with chronic HCV and the combination of an HLA-B allele with an aspartate at residue 114 and the tapasin G allele also had stronger CD8+ T-cell responses (P=0.02, OR=2.58, 95% CI-1.05-6.5). Tapasin alleles contribute to the outcome of HCV infection by synergizing with polymorphisms at HLA-B in a population-specific manner. This polymorphism may be relevant for peptide vaccination strategies against HCV infection.

Heterosexual Anal Intercourse among Men in Long Beach, California. Hess KL, Reynolds GL, Fisher DG. J Sex Res. 2013 Sep 11. [Epub ahead of print].
Anal intercourse poses a greater risk for human immunodeficiency virus (HIV) transmission than vaginal intercourse, and in recent years there has been a growing understanding that heterosexual anal intercourse (HAI) is not uncommon. However, the majority of the anal intercourse literature has focused on men who have sex with men. The little research on HAI has mostly looked at women, with limited work among men. This analysis examined the association between HAI and high-risk behaviors (N = 1,622) and sexual sensation seeking (N = 239) in a sample of men recruited from 2001 to 2012 in Long Beach, California. Almost half of the sample was non-

Hispanic Black. The median age was 42 years, 42% were homeless, and 20% reported recent HAI. Men who reported HAI were likely to be Hispanic, were likely to be homeless, had a male partner, engaged in sex exchange, and used cocaine or amphetamines during sex. Men who reported HAI scored higher on the Sexual Sensation Seeking scale. This research supports other work showing the relationship between HAI and high-risk behaviors. More important, it contributes new knowledge by demonstrating the association between HAI and sexual sensation seeking. This research highlights the importance of personality traits when trying to understand sexual behavior and when developing HIV prevention interventions.

Cyclosporine-Inhibitable Blood-Brain Barrier Drug Transport Influences Clinical Morphine Pharmacodynamics. Meissner K, Avram MJ, Yermolenka V, Francis AM, Blood J, Kharasch ED. Anesthesiology. 2013 Oct; 119(4): 941-953. Doi :10.1097/ALN. 0b013e3182a05bd3.

The blood-brain barrier is richly populated by active influx and efflux transporters influencing brain drug concentrations. Morphine, a drug with delayed clinical onset, is a substrate for the efflux transporter P-glycoprotein in vitro and in animals. This investigation tested whether morphine is a transporter substrate in humans. Fourteen healthy volunteers received morphine (0.1 mg/kg, 1-h IV infusion) in a crossover study without (control) or with the infusion of validated P-glycoprotein inhibitor cyclosporine (5 mg/kg, 2-h infusion). Plasma and urine morphine and morphine glucuronide metabolite concentrations were measured by mass spectrometry. Morphine effects were measured by miosis and analgesia. Cyclosporine minimally altered morphine disposition, increasing the area under the plasma morphine concentration versus time curve to 100 ± 21 versus 85 ± 24 ng/ml·h ($P < 0.05$) without changing maximum plasma concentration. Cyclosporine enhanced (3.2 ± 0.9 vs. 2.5 ± 1.0 mm peak) and prolonged miosis, and increased the area under the miosis-time curve (18 ± 9 vs. 11 ± 5 mm·h), plasma effect-site transfer rate constant (ke0, median 0.27 vs. 0.17 h), and maximum calculated effect-site morphine concentration (11.5 ± 3.7 vs. 7.6 ± 2.9 ng/ml; all $P < 0.05$). Analgesia testing was confounded by cyclosporine-related pain. Morphine is a transporter substrate at the human blood-brain barrier. Results suggest a role for P-glycoprotein or other efflux transporters in brain morphine access, although the magnitude of the effect is small, and unlikely to be a major determinant of morphine clinical effects. Efflux may explain some variability in clinical morphine effects.

Mechanism Of Autoinduction Of Methadone N-Demethylation In Human Hepatocytes Campbell SD, Crafford A, Williamson BL, Kharasch ED. Anesth Analg. 2013 Jul; 117(1): 52-60. doi: 10.1213/ANE.0b013e3182918252. Epub 2013 Jun 3.

There is considerable interindividual and intraindividual variability in methadone metabolism and clearance. Methadone dosing is particularly challenging during initiation of therapy, because of time-dependent increases in hepatic clearance (autoinduction). Although methadone N-demethylation is catalyzed in vitro by cytochrome P4502B6 (CYP2B6) and CYP3A4, and clearance in vivo depends on CYP2B6, mechanism(s) of autoinduction are incompletely understood. In this investigation, the authors determined mechanism(s) of methadone autoinduction using human hepatocytes. Fresh human hepatocytes were exposed to 0.1 to 10 μM methadone for 72 hours. Cells were washed and methadone N-demethylation assessed. CYP2B6, CYP3A4, and CYP3A5 messenger RNA (mRNA), protein expression (by gel-free high-performance liquid chromatography mass spectrometry) and catalytic activity (bupropion

hydroxylation and alfentanil dealkylation for CYP2B6 and CYP3A4/5, respectively) were measured. Mechanisms of CYP induction were characterized using pregnane X receptor and constitutive androstane receptor reporter gene assays. Methadone (10 μM) increased methadone N-demethylation 2-fold, CYP2B6 and CYP3A4 mRNA 3-fold, and protein expression 2-fold. CYP3A5 mRNA was unchanged. CYP2B6 and CYP3A4/5 activities increased 2-fold. Induction by methadone enantiomers (R-methadone versus S-methadone) did not differ. Induction was relatively weak compared with maximum induction by phenobarbital and rifampin. Lower methadone concentrations had smaller effects. Methadone was an agonist for the pregnane X receptor but not the constitutive androstane receptor. Methadone caused concentration-dependent autoinduction of methadone N-demethylation in human hepatocytes, related to induction of CYP2B6 and CYP3A4 mRNA expression, protein expression, and catalytic activity. Induction was related to pregnane X receptor but not constitutive androstane receptor activation. These in vitro findings provide mechanistic insights into clinical autoinduction of methadone metabolism and clearance.

High-Sensitivity Analysis Of Buprenorphine, Norbuprenorphine, Buprenorphine Glucuronide, And Norbuprenorphine Glucuronide In Plasma and Urine By Liquid Chromatography-Mass Spectrometry. Regina KJ, Kharasch ED. J Chromatogr B Analyt Technol Biomed Life Sci. 2013 Nov 15; 939: 23-31. doi: 10.1016/j.jchromb.2013.09.004. Epub 2013 Sep 8.

A new method using ultra-fast liquid chromatography and tandem mass spectrometry (UFLC-MS/MS) was developed for the simultaneous determination of buprenorphine and the metabolites norbuprenorphine, buprenorphine-3β-glucuronide, and norbuprenorphine-3β-glucuronide in plasma and urine. Sample handling, sample preparation and solid-phase extraction procedures were optimized for maximum analyte recovery. All four analytes of interest were quantified by positive ion electrospray ionization tandem mass spectrometry after solid-phase microextraction. The lower limits of quantification in plasma were 1pg/mL for buprenorphine and buprenorphine glucuronide, and 10pg/mL for norbuprenorphine and norbuprenorphine glucuronide. The lower limits of quantitation in urine were 10pg/mL for buprenorphine, norbuprenorphine and their glucuronides. Overall extraction recoveries ranged from 68-100% in both matrices. Interassay precision and accuracy was within 10% for all four analytes in plasma and within 15% in urine. The method was applicable to pharmacokinetic studies of low-dose buprenorphine.

Illicit Drug Use and Cardiometabolic Disease Risk: An Analysis Of 2005-2008 National Health and Nutrition Examination Survey Data. Vidot DC, Arheart KL, Prado G, Bandstra ES, Messiah SE. Int J Clin Pract. 2013 Nov; 67(11): 1173-1181. doi: 10.1111/ijcp.12189.

The purpose of thi study was to explore the association between illicit drug use (IDU) and cardiometabolic disease risk factors (CDRF) in a nationally representative sample of adults. The 2005-2008 National Health and Nutrition Examination Surveys data from 20- to 45-year-old adults (n = 8738) were utilized to analyze the relationship between IDU (ever used, repeated use and current use) and CDRF (hyperlipidemia, hyperinsulinemia, hypertension, elevated C-reactive protein, body mass index, waist circumference and cigarette use) via chi square and logistic regression analyses. Age, gender, race/ethnicity, education level, poverty to income ratio (PIR), and alcohol use were included as confounders in the models. Individuals who reported drug use (DU) at least once in lifetime were more likely to have CDRF than non-DU (NDU) (OR = 1.3,

p = 0.004). Females with DU, IDU at least once in lifetime, and with repeated IDU were about 1.5 times more likely than their NDU counterparts to have CDRF ($p < 0.0001$, $p = 0.02$, $p = 0.02$, respectively). Results from this study suggest that healthcare professionals should be aware that patients with a history of DU may be at heightened risk for cardiometabolic disease. Females in particular have a heightened cluster of CDRF across drug-use categories.

Changes In Weight and Co-Morbidities Among Adolescents Undergoing Bariatric Surgery: 1-Year Results From the Bariatric Outcomes Longitudinal Database. Messiah SE, Lopez-Mitnik G, Winegar D, Sherif B, Arheart KL, Reichard KW, Michalsky MP, Lipshultz SE, Miller TL, Livingstone AS, de la Cruz-Muñoz N. Surg Obes Relat Dis. 2013 Jul-Aug;9(4):503-13. doi: 10.1016/j.soard.2012.03.007. Epub 2012 Mar 28.

Bariatric surgery is 1 of the few effective treatments of morbid obesity. However, the weight loss and other health-related outcomes for this procedure in large, diverse adolescent patient populations have not been well characterized. The authors' objective was to analyze the prospective Bariatric Outcomes Longitudinal Database (BOLD) to determine the weight loss and health related outcomes in adolescents. The BOLD data are collected from 423 surgeons at 360 facilities in the United States. The main outcome measures included the anthropometric and co-morbidity status at baseline (n = 890) and at 3 (n = 786), 6 (n = 541), and 12 (n = 259) months after surgery. Adolescents (75% female; 68% non-Hispanic white, 14% Hispanic, 11% non-Hispanic black, and 6% other) aged 11 to 19 years were included in the present analyses. The overall 1-year mean weight loss for those who underwent gastric bypass surgery was more than twice that of those who underwent adjustable gastric band surgery (48.6 versus 20 kg, $P < .001$). Similar results were found for all other anthropometric changes and comparisons within 1 year between surgery types ($P < .001$). In general, the gastric bypass patients reported more improvement than the adjustable gastric band patients in co-morbidities at 1 year after surgery. A total of 45 readmissions occurred among gastric bypass patients and 10 among adjustable gastric band patients, with 29 and 8 reoperations required, respectively. The weight loss at 3, 6, and 12 months after surgery is approximately double in adolescent males and females who underwent gastric bypass surgery versus those who underwent adjustable gastric band surgery. Bariatric surgery can safely and substantially reduce weight and related co-morbidities in morbidly obese adolescents for ≥1 year.

The Lifetime Prevalence Of Anabolic-Androgenic Steroid Use and Dependence In Americans: Current Best Estimates. Pope HG Jr, Kanayama G, Athey A, Ryan E, Hudson JI, Baggish A. Am J Addict. 2013 Sep 20. doi: 10.1111/j.1521-0391.2013.12118.x. [Epub ahead of print].

Although various surveys have tracked the prevalence of anabolic-androgenic steroid (AAS) use in American teenagers and young adults, no recent surveys have assessed the lifetime prevalence of AAS use in Americans overall. The authors therefore analyzed serial youth-survey data to derive estimates of the lifetime prevalence of AAS use in the current American general population. They first determined the distribution of age of onset of AAS use, based on pooled data from nine studies. Using this distribution, they then developed equations to project the eventual lifetime prevalence of AAS use among young survey respondents, once they aged and completed the period of risk for initiating AAS. They similarly calculated the denominator of lifetimes of risk for AAS use in the total American population. They next applied these equations to four independent national youth datasets to derive current American general-population

estimates for lifetime AAS use. Finally, using data from 10 pooled studies, they estimated the lifetime prevalence of AAS dependence among AAS users. Age-of-onset studies consistently showed that AAS use begins later than most drugs, with only 22% of users (95% confidence interval: 19-25%) starting before age 20. Applying the age-of-onset findings to national youth datasets, the authors estimated that among Americans currently age 13-50 years, 2.9-4.0 million have used AAS. Within this group, roughly 1 million may have experienced AAS dependence. Although subject to various limitations, our estimation techniques suggest a surprisinigly high prevalence of AAS use and dependence among Americans.

Addressing Health Disparities among Men: Demographic, Behavioral and Clinical Characteristics of Men who have Sex with Men Living in Puerto Rico. Colón-López V, Soto-Salgado M, Rodríguez-Díaz C, Suárez EL, Pérez CM. Sex Res Social Policy. 2013 Sep 1; 10(3). doi: 10.1007/s13178-013-0130-9.
The objective of this study was to compare sociodemographic, behavioral and clinical characteristics associated with HIV among Men who have sex with Men (MSM) and men who have sex with women (MSW) in Puerto Rico. Data from a population-based cross-sectional study in PR (2005-2008) was analyzed. Descriptive statistics were used to describe the study sample and bivariate analyses were performed to identify differences of sociodemographic, behavioral and clinical characteristics between MSM and MSW. Exact logistic regression models adjusting for age were constructed for each risk behavior associated to MSM in bivariate analysis. Of the 674 men interviewed, 6.1% (n=41) reported ever having sex with men. Age-adjusted logistic regression models indicated that MSM were significantly more likely than MSW to have first sexual intercourse before the age of 15 (POR=2.6; 95%CI= 1.3, 5.3) and have at least 10 lifetime sex partners (POR=2.8; 95%CI= 1.4,5.9). Also, MSM were significantly more likely to report lifetime use of marihuana (POR=2.7; 95%CI= 1.3,5.8), cocaine (POR=2.5; 95%CI= 1.2,5.0), amphetamines (POR=3.8; 95%CI= 1.4,9.2) and sedatives or tranquilizers (POR=3.3; 95%CI= 1.4,7.2). Also, MSM were 13 times more likely to be HIV seropositive as compared to MSW (POR=13.3; 95%CI=1.7,102.0). In this population-based sample of men living in Puerto Rico, self-reported same-sex behavior is strongly associated with HIV, and other behavioral factors associated with HIV. Future targeted research is still necessary for the development of intervention programs among MSM in Puerto Rico.

Faldaprevir Combined With Pegylated Interferon Alfa-2a and Ribavirin In Treatment-Naïve Patients With Chronic Genotype1 HCV: SILEN-C1 Trial. Sulkowski MS, Bourlière M, Bronowicki JP, Asselah T, Pawlotsky JM, Shafran SD, Pol S, Mauss S, Larrey D, Datsenko Y, Stern JO, Kukolj G, Scherer J, Nehmiz G, Steinmann GG, Böcher WO. Hepatology. 2013 Jun; 57(6): 2155-2163. doi: 10.1002/hep.26386.
Faldaprevir (BI 201335) is a potent, hepatitis C virus (HCV) NS3/4A protease inhibitor with pharmacokinetic properties supportive of once-daily (QD) dosing. Four hundred and twenty-nine HCV genotype (GT)-1 treatment-naïve patients without cirrhosis were randomized 1:1:2:2 to receive 24 weeks of pegylated interferon alfa-2a and ribavirin (PegIFN/RBV) in combination with placebo, faldaprevir 120 mg QD with 3 days of PegIFN/RBV lead-in (LI), 240 mg QD with LI, or 240 mg QD without LI, followed by an additional 24 weeks of PegIFN/RBV. Patients in the 240 mg QD groups achieving maintained rapid virologic response (mRVR; viral load [VL] <25 IU/mL at week 4 and undetectable at weeks 8-20) were rerandomized to cease all treatment at week 24 or continue receiving PegIFN/RBV up to week 48. VL was measured by Roche

TaqMan. Sustained virologic response (SVR) rates were 56%, 72%, 72%, and 84% in the placebo, faldaprevir 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD groups. Ninety-two percent of mRVR patients treated with faldaprevir 240 mg QD achieved SVR, irrespective of PegIFN/RBV treatment duration. Eighty-two percent of GT-1a patients who received faldaprevir 240 mg QD achieved SVR versus 47% with placebo. Mild gastrointestinal disorders, jaundice resulting from isolated unconjugated hyperbilirubinemia, and rash or photosensitivity were more common in the active groups than with placebo. Discontinuations resulting from adverse events occurred in 4%, 11%, and 5% of patients treated with 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD of faldaprevir versus 1% with placebo. Faldaprevir QD with PegIFN/RBV achieved consistently high SVR rates with acceptable tolerability and safety at all dose levels. The 120 and 240 mg QD doses are currently undergoing phase 3 evaluation.

Hepatitis C Virus Maintains Infectivity for Weeks after Drying on Inanimate Surfaces at Room Temperature: Implications for Risks of Transmission. Elijah Painstil Elijah Paintsil1, Mawuena Binka2, Amisha Patel2, Brett D. Lindenbach3, and Robert Heimer. Journal of Infectious Diseases, J Infect Dis. 2013 Nov 23. [Epub ahead of print].
Healthcare workers may come into contact with fomites containing infectious HCV during preparation of plasma, or following placement or removal of venous lines. Similarly, injection drugs users may come into contact with fomites. Hypothesizing that prolonged viability of HCV in fomites may contribute significantly to incidence; the authors determined the longevity of virus infectivity and the effectiveness of antiseptics. They determined the volume of drops misplaced during transfer of serum or plasma. Aliquots equivalent to the maximum drop volume of plasma spiked with 2a HCV reporter virus were loaded into 24-well plates. Plates were stored uncovered at three temperatures: 4°, 22°, and 37°C for up to 6 weeks before viral infectivity was determined in a microculture assay. The mean volume of an accidental drop was 29 µl (min - max of 20 - 33 µl). At storage temperatures 4° and 22°C, the authors recovered viable HCV from the low titer spots for up to 6 weeks of storage. The rank order of HCV virucidal activity of commonly used antiseptics was bleach (1:10) > cavicide (1:10) > ethanol (70%). The hypothesis of potential transmission from fomites was supported by the experimental results. The anti-HCV activity of commercial antiseptics varied.

Cognitive Deficits In Long-Term Anabolic-Androgenic Steroid Users. Kanayama G, Kean J, Hudson JI, Pope HG Jr. Drug Alcohol Depend. 2013 Jun 1; 130(1-3): 208-214. doi: 10.1016/j.drugalcdep.2012.11.008. Epub 2012 Dec 14.
Millions of individuals worldwide have used anabolic-androgenic steroids (AAS) to gain muscle or improve athletic performance. Recently, in vitro investigations have suggested that supraphysiologic AAS doses cause apoptosis of neuronal cells. These findings raise the possibility, apparently still untested, that humans using high-dose AAS might eventually develop cognitive deficits. The authors administered five cognitive tests from the computerized CANTAB battery (Pattern Recognition Memory, Verbal Recognition Memory, Paired Associates Learning, Choice Reaction Time, and Rapid Visual Information Processing) to 31 male AAS users and 13 non-AAS-using weightlifters age 29-55, recruited and studied in May 2012 in Middlesbrough, UK. Testers were blinded to participants' AAS status and other historical data. Long-term AAS users showed no significant differences from nonusers on measures of response speed, sustained attention, and verbal memory. On visuospatial memory, however, AAS users performed significantly more poorly than nonusers, and within the user

group, visuospatial performance showed a significant negative correlation with total lifetime AAS dose. These were large effects: on Pattern Recognition Memory, long-term AAS users underperformed nonusers by almost one standard deviation, based on normative population scores (adjusted mean difference in z-scores=0.89; p=0.036), and performance on this test declined markedly with increasing lifetime AAS dose (adjusted change in z-score=-0.13 per 100g of lifetime AAS dose; p=0.002). These results remained stable in sensitivity analyses addressing potential confounding factors. These preliminary findings raise the ominous possibility that long-term high-dose AAS exposure may cause cognitive deficits, notably in visuospatial memory.

SERVICES RESEARCH

A Randomized Trial Of A Hepatitis Care Coordination Model In Methadone Maintenance Treatment. Masson CL, Delucchi KL, McKnight C, Hettema J, Khalili M, Min A, Jordan AE, Pepper N, Hall J, Hengl NS, Young C, Shopshire MS, Manuel JK, Coffin L, Hammer H, Shapiro B, Seewald RM, Bodenheimer Jr, HC, Sorensen JL, Des Jarlais DC, Perlman DC. Am J Public Health. 2013; 103(10): e81-e88.
The authors evaluated the efficacy of a hepatitis care coordination intervention to improve linkage to hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccination and clinical evaluation of hepatitis C virus (HCV) infection among methadone maintenance patients. They conducted a randomized controlled trial of 489 participants from methadone maintenance treatment programs in San Francisco, California, and New York City from February 2008 through June 2011. They randomized participants to a control arm (n = 245) and an intervention arm (n = 244), which included on-site screening, motivational-enhanced education and counseling, on-site vaccination, and case management services. Compared with the control group, intervention group participants were significantly more likely (odds ratio [OR] = 41.8; 95% confidence interval [CI] = 19.4, 90.0) to receive their first vaccine dose within 30 days and to receive an HCV evaluation within 6 months (OR = 4.10; 95% CI = 2.35, 7.17). A combined intervention adherence outcome that measured adherence to HAV-HBV vaccination, HCV evaluation, or both strongly favored the intervention group (OR = 8.70; 95% CI = 5.56, 13.61). Hepatitis care coordination was efficacious in increasing adherence to HAV-HBV vaccination and HCV clinical evaluation among methadone patients.

Organizational Implementation of Evidence-Based Substance Abuse Treatment in Racial and Ethnic Minority Communities. Guerrero EG, He A, Kim A, Aarons GA. Adm Policy Ment Health. 2013 Sep 18. [Epub ahead of print].
The authors evaluated organizational factors associated with the implementation of contingency management treatment (CMT) and medication-assisted treatment (MAT) in substance abuse treatment (SAT) programs serving racial and ethnic minority communities. Analysis of cross-sectional data collected in 2010-2011 from a random sample of 148 publicly funded SAT programs showed that accepting private insurance was positively associated with CMT and MAT implementation, whereas larger programs were associated with greater implementation of MAT. Supervisorial openness to and expectations about implementing evidence-based practices (EBPs) and attributes for change were strongly associated with CMT, whereas the interactions between openness to EBPs and programs that accept private insurance and that are governed by parent organizations were positively associated with MAT. These external expectations and managerial attitudes supported the implementation of psychosocial and pharmacotherapy treatments in SAT. Implications for improving standards of care in minority communities are discussed.

Managing Psychiatric Comorbidity within Versus Outside of Methadone Treatment Settings: A Randomized and Controlled Evaluation. Brooner RK, Kidorf MS, King VL, Peirce J, Neufeld K, Stoller K, Kolodner K. Addiction. 2013; 108(11): 1942-1951.
Integrating psychiatric services within substance abuse treatment settings is a promising service delivery model, but has not been evaluated using random assignment to psychiatric treatment setting and controlled delivery of psychiatric care. This study evaluates the efficacy of on-site and integrated psychiatric service delivery in an opioid-agonist treatment program on psychiatric

and substance use outcomes. Participants at the Addiction Treatment Services (ATS) were assigned randomly to receive on-site and integrated substance abuse and psychiatric care (on-site: n = 160) versus off-site and non-integrated substance abuse and psychiatric care (off-site: n = 156), and observed for 1 year. On-site participants received all psychiatric care within the substance abuse program by the same group of treatment providers. The same type and schedule of psychiatric services were available to off-site participants at a community psychiatry program. All participants received routine methadone maintenance at the ATS program in Baltimore, Maryland, USA. Participants were opioid-dependent men and women with at least one comorbid psychiatric disorder, as assessed by the Structured Clinical Interview for DSM-IV and confirmed by expert clinical reappraisal. Outcomes included psychiatric service utilization and retention, Hopkins Symptom Checklist Global Severity Index (GSI) change scores and urinalysis test results. On-site participants were more likely to initiate psychiatric care 96.9 to 79.5%; $P < 0.001$), remain in treatment longer (195.9 versus 101.9 days; $P < 0.001$), attend more psychiatrist appointments (12.9 versus 2.7; $P < 0.001$) and have greater reductions in GSI scores On-site and integrated psychiatric and substance misuse services in a methadone treatment setting might improve psychiatric outcomes compared with off-site and non-integrated substance misuse and psychiatric care. However, this might not translate into improved substance misuse outcomes.

A Comparison of Modified Directly Observed Therapy to Standard Care for Chronic Hepatitis C. Cioe PA, Stein MD, Promrat K, Friedmann PD.. J Community Health. 2013; 38(4): 679-684.

Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States. Effective treatments are available, however adherence to treatment is challenging. Modified directly observed therapy (mDOT) with weekly administration of pegylated interferon might improve adherence and outcomes for patients infected with chronic HCV. The purpose of this study was to compare two treatment protocols and examine predictors of sustained virologic response (SVR). This retrospective review compares HCV treatment outcomes in two outpatient clinics at an urban academic medical center. Gastroenterology fellows provided standard treatment (SC) in one clinic; a nurse practitioner administered weekly pegylated interferon injections weekly in a primary care clinic. All patients received oral ribavirin. Data was extracted from the medical records of all treated patients over a 5-year period. 155 treatment-naïve, chronically infected HCV patients were treated. Ninety-seven patients received mDOT treatment and 58 received standard care. Mean age was 46 years. Genotype 1 represented 59 % of the sample. The mDOT patients were significantly more likely to be younger (44 vs. 50 years), have a history of injection drug use (93.1 vs. 50.0 %), and be HIV-infected (13.5 vs. 2 %) compared to SC patients. The overall SVR rate was 45.2 % and did not differ between the groups in unadjusted analyses ($p = 0.95$). Genotype was the only predictor of SVR. Patients treated by nurse practitioners trained in HCV care and seen weekly for interferon injections have comparable treatment outcomes to patients treated by specialists.

Children of Treated Substance-Abusing Mothers: A 10-Year Prospective Study. Hser Y-I, Evans E, Li L, Metchik-Gaddis A, Messina N. Clin Child Psychol Psychiatry. 2013 May 15. [Epub ahead of print].

This study examined children of substance-abusing mothers approximately 10 years after mothers' admission to drug abuse treatment, and identified maternal characteristics that may be

risk factors for child behavior problems on the Child Behavior Checklist. Data were obtained from 396 mothers who were included in a sample consecutively admitted to 44 treatment programs in 13 California counties during 2000-2002. The Addiction Severity Index was administered at both intake and follow-up. Each mother reported on one child 6-17 years of age. All of the children had been exposed to drugs, either in utero or postnatally. At follow-up about 22% of the children demonstrated borderline or clinical range problem behaviors. Child behavior problems were related significantly to the mothers' ethnicity (lower among Hispanics relative to white), and problem severity in family/social relationship and mental health, marginally related to her prior medical/health problem, and not related to severity of alcohol, drug, legal and employment problems. Assisting mothers to address their family/social relationship and psychological problems may have an added value to prevent or reduce behavioral problems of their children.

Capacity of US Drug Treatment Facilities to Provide Evidence-Based Tobacco Treatment. Hunt JJ, Gajewski BJ, Jiang Y, Cupertino AP, Richter KP. Am J Public Health. 2013; 103(10): 1799-1801.

Although people with drug problems consume a large proportion of cigarettes smoked in the United States, few drug treatment facilities offer tobacco treatment. The authors' analysis of 405 facilities showed that most had the skills but few had policies, leadership, or financial resources to provide evidence-based tobacco treatment. For-profits reported significantly fewer tobacco treatment resources than nonprofits. The Affordable Care and Mental Health Parity Acts will improve treatment access for drug-dependent persons. To realize these acts' full promise, policymakers should ensure that clients have access to tobacco treatment.

Varenicline for Smoking Cessation among Methadone-Maintained Smokers: A Randomized Clinical Trial. Stein MD, Caviness CM, Kurth ME, Audet D, Olson J, Anderson BJ. Drug Alcohol Depend. 2013 Dec 1;133(2):486-93. doi: 10.1016/j.drugalcdep.2013.07.005. Epub 2013 Aug 14.

With smoking rates far exceeding the general population, methadone-maintained (MMT) opiate-dependent smokers experience high rates of tobacco-related health consequences. Previous treatment studies have used nicotine replacement and produced low quit rates. The authors test, using a three-group randomized design, the efficacy of varenicline versus placebo, in comparison with nicotine replacement therapy (NRT) that combines nicotine patch prescription plus ad libitum nicotine rescue, for smoking cessation. They recruited methadone-maintained smokers from nine treatment centers in southern New England and provided six months of treatment, and a minimal behavioral intervention at baseline (NCI's 5A's). Outcomes included carbon monoxide (CO) confirmed 7-day point smoking cessation prevalence at 6 months and self-reported change in mean cigarettes per day. The 315 participants had a mean age of 40, with 50% male and 79% non-Hispanic White, smoked an average of 19.6 (Plus/Minus10.4) cigarettes/day, and had a mean daily methadone dose of 109mg. Intent-to-treat analyses, with missing considered to be smoking, showed the rate of CO-confirmed 7-day abstinence at 6-months was 5.4% overall, with varenicline 3.7% compared to placebo 2.2%, and NRT 8.3% ($p>.05$). Adherence rates during the 7-days immediately prior to 6-month assessment were 34.2% in varenicline, 34.4% in placebo, and 48.8% in NRT. Between baseline and 6-months there was an overall self-reported mean reduction of 8.3 cigarettes/day. Varenicline did not

increase quit rates over placebo. Smoking cessation rates in methadone-maintained smokers are low and novel treatment strategies are required.

Post-Release Substance Abuse Outcomes Among HIV-Infected Jail Detainees: Results from a Multisite Study. Krishnan A, Wickersham JA, Chitsaz E, Springer SA, Jordan AO, Zaller N, Altice FL. AIDS Behav. 2013; 17 Suppl 2: 171-180.
HIV-infected individuals with substance use disorders have a high prevalence of medical and psychiatric morbidities that complicate treatment. Incarceration further disrupts healthcare access and utilization. Without appropriate diagnosis and treatment, drug relapse upon release exceeds 85%, which contributes to poor health outcomes. A prospective cohort of 1,032 HIV-infected jail detainees were surveyed in a ten-site demonstration project during incarceration and six-months post-release, in order to examine the effect of predisposing factors, enabling resources and need factors on their subsequent drug use. Homelessness, pre-incarceration cocaine and opioid use, and high drug and alcohol severity were significantly associated with cocaine and opioid relapse. Substance abuse treatment, though poorly defined, did not influence post-release cocaine and opioid use. An approach that integrates multiple services, simultaneously using evidence-based substance abuse, psychiatric care, and social services is needed to improve healthcare outcomes for HIV-infected persons transitioning from jails to the community.

Correlates of Retention in HIV Care After Release from Jail: Results from a Multi-site Study. Althoff AL, Zelenev A, Meyer JP, Fu J, Brown S-E,; Vagenas P, Avery AK, Cruzado-Quinones J, Spaulding AC, Altice FL. AIDS Behav. 2013; 17 Suppl 2 : 156-170.
Retention in care is key to effective HIV treatment, but half of PLWHA in the US are continuously engaged in care. Incarcerated individuals are an especially challenging population to retain, and empiric data specific to jail detainees is lacking. The authors prospectively evaluated correlates of retention in care for 867 HIV-infected jail detainees enrolled in a 10-site demonstration project. Sustained retention in care was defined as having a clinic visit during each quarter in the 6 month post-release period. The following were independently associated with retention: being male (AOR = 2.10, $p \leq 0.01$), heroin use (AOR 1.49, $p = 0.04$), having an HIV provider (AOR 1.67, $p = 0.02$), and receipt of services: discharge planning (AOR 1.50, $p = 0.02$) and disease management session (AOR 2.25, $p \leq 0.01$) during incarceration; needs assessment (AOR 1.59, $p = 0.02$), HIV education (AOR 2.03, $p \leq 0.01$), and transportation assistance (AOR 1.54, $p = 0.02$) after release. Provision of education and case management services improve retention in HIV care after release from jail.

Longitudinal Twin Study of Borderline Personality Disorder Traits and Substance Use in Adolescence: Developmental Change, Reciprocal Effects, and Genetic and Environmental Influences. Bornovalova MA, Hicks BM, Iacono WG, McGue M. Personal Disord. 2013; 4(1): 23-32.
Although the comorbidity between borderline personality disorder (BPD) and substance abuse is well established, there are few longitudinal studies that have examined its developmental origins or whether the comorbidity is due to common genetic or environmental risk factors. To fill this gap, the authors used a large sample of female adolescent twins (N = 1,280) to examine the developmental course, reciprocal influences, and the genetic and environmental factors underlying the co-occurrence of BPD traits and substance use from age 14 to 18. Rank-order stability was moderate to high for both BPD traits ($r = .58$) and substance use ($r = .51$), whereas

mean levels of substance use increased substantially from age 14 to 18 (d = 0.77) and BPD traits showed a small decline (d = -0.21). BPD traits and substance use exhibited concurrent and prospective associations; however, the longitudinal associations dropped to non-significance after accounting for the temporal stability of each trait. Twin analyses revealed that shared environmental factors accounted for the association between BPD traits and substance use at age 14, but genetic factors accounted for the association at age 18. These results indicate that, at least in adolescence, the comorbidity between BPD traits and substance use is a consequence of common risk factors rather than due to one being a casual antecedent of the other.

Tests of A Direct Effect of Childhood Abuse on Adult Borderline Personality Disorder Traits: A Longitudinal Discordant Twin Design. Bornovalova MA, Huibregtse BM, Hicks BM, Keyes M, McGue M, Iacono W. J Abnorm Psychol. 2013; 122(1): 180-194.
The authors used a longitudinal twin design to examine the causal association between sexual, emotional, and physical abuse in childhood (before age 18) and borderline personality disorder (BPD) traits at age 24 using a discordant twin design and biometric modeling. Additionally, they examined the mediating and moderating effects of symptoms of childhood externalizing and internalizing disorders on the link between childhood abuse and BPD traits. Although childhood abuse, BPD traits, and internalizing and externalizing symptoms were all correlated, the discordant twin analyses and biometric modeling showed little to no evidence that was consistent with a causal effect of childhood abuse on BPD traits. Instead, these results indicate that the association between childhood abuse and BPD traits stems from common genetic influences that, in some cases, also overlap with internalizing and externalizing disorders. These findings are inconsistent with the widely held assumption that childhood abuse causes BPD, and they suggest that BPD traits in adulthood are better accounted for by heritable vulnerabilities to internalizing and externalizing disorders.

Methadone Dose at the Time of Release from Prison Significantly Influences Retention in Treatment: Implications from a Pilot Study of HIV-Infected Prisoners Transitioning to the Community in Malaysia. Wickersham JA, Zahari MM, Azar MM, Kamarulzaman A, Altice FL. Drug Alcohol Depend. 2013; 132(1-2): 378-382.
The objective of this study was to evaluate the impact of methadone dose on post-release retention in treatment among HIV-infected prisoners initiating methadone maintenance treatment (MMT) within prison. Thirty HIV-infected prisoners meeting DSM-IV pre-incarceration criteria for opioid dependence were enrolled in a prison-based, pre-release MMT program in Klang Valley, Malaysia; 3 died before release from prison leaving 27 evaluable participants. Beginning 4 months before release, standardized methadone initiation and dose escalation procedures began with 5mg daily for the first week and 5mg/daily increases weekly until 80 mg/day or craving was satisfied. Participants were followed for 12 months post-release at a MMT clinic within 25 kilometers of the prison. Kaplan-Meier survival analysis was used to evaluate the impact of methadone dose on post-release retention in treatment. Methadone dose ≥80 mg/day at the time of release was significantly associated with retention in treatment. After 12 months of release, only 21.4% of participants on <80 mg were retained at 12 months compared to 61.5% of those on ≥80 mg (Log Rank $\chi(2)=(1,26)$ 7.6, $p<0.01$). Higher doses of MMT at time of release are associated with greater retention on MMT after release to the community. Important attention should be given to monitoring and optimizing MMT doses to address cravings and side effects prior to community re-entry from prisons.

Optimizing Care for HIV-Infected People Who Use Drugs: Evidence-Based Approaches to Overcoming Healthcare Disparities. Meyer JP, Althoff AL Altice FL. Clin Infect Dis. 2013; 57(9): 1309-1317.
Substance use disorders (SUDs) and Human Immunodeficiency Virus (HIV) are pervasive epidemics that synergize, resulting in negative outcomes for HIV-infected people who use drugs (PWUDs). The expanding epidemiology of substance use demands a parallel evolution of the HIV specialist-beyond HIV to diagnosis and management of comorbid SUDs. The purpose of this paper is to describe healthcare disparities for HIV-infected PWUDs along each point of a continuum of care, and to suggest evidence-based strategies for overcoming these healthcare disparities. Despite extensive dedicated resources and availability of antiretroviral therapy (ART) in the United States, PWUDs continue to experience delayed HIV diagnosis, reduced entry into and retention in HIV care, delayed initiation of ART, and inferior HIV treatment outcomes. Overcoming these healthcare disparities requires integrated packages of clinical, pharmacological, behavioral, and social services, delivered in ways that are cost-effective and convenient and include, at a minimum, screening for and treatment of underlying SUDs.

Longitudinal Changes in Engagement In Care and Viral Suppression for HIV-Infected Injection Drug Users. Westergaard RP, Hess T, Astemborski J, Mehta SH, Kirk GD. AIDS. 2013; 27(16): 2559-2566.
The objective of this study was to examine temporal trends and predictors of linkage to HIV care, longitudinal retention in care and viral suppression among injection drug users (IDUs) infected with HIV. Thus was a community-based, prospective cohort study. The authors prospectively studied 790 HIV-infected IDUs participating in the AIDS Linked to the Intravenous Experience (ALIVE) study from 1998 through 2011. IDUs were considered linked to care if they attended any HIV care visit during follow-up and retained in care if they reported HIV clinic attendance at every semi-annual study visit. They used logistic regression to identify predictors of poor retention in care and failure to achieve sustained viral suppression in response to ART. Of 790 HIV-infected IDUs studied, 740 (93.6%) were ever linked to care. The majority of IDUs (76.7%) received ART at some point during observation and of these, most (85.4%) achieved viral suppression. However, over a median of 8.7 years of follow-up, only 241 (30.5%) IDUs were continuously retained with no 6-month lapses in HIV care and only 63 (10.2%) had sustained viral suppression at every study visit after first receiving ART. Suboptimal engagement in care was associated with poor access to medical care, active drug use, and incarceration. Compared with national estimates of retention in care and virologic suppression in the United States, IDUs are substantially less likely to remain fully engaged in HIV care. Strategies to optimize HIV care should acknowledge the elevated risk of poor engagement in care among IDUs.

Randomized, Community-Based Pharmacy Intervention to Expand Services Beyond Sale of Sterile Syringes to Injection Drug Users in Pharmacies in New York City. Crawford N D, Amesty S, Rivera AV, Harripersaud K, Turner A, Fuller CM. Am J Public Health. 2013; 103(9): 1579-1582.
Structural interventions may help reduce racial/ethnic disparities in HIV. In 2009 to 2011, the authors randomized pharmacies participating in a nonprescription syringe access program in minority communities to intervention (pharmacy enrolled and delivered HIV risk reduction information to injection drug users [IDUs]), primary control (pharmacy only enrolled IDUs), and

secondary control (pharmacy did not engage IDUs). Intervention pharmacy staff reported more support for syringe sales than did control staff. An expanded pharmacy role in HIV risk reduction may be helpful.

Contribution of Substance Use Disorders on HIV Treatment Outcomes and Antiretroviral Medication Adherence Among HIV-Infected Persons Entering Jail. Chitsaz E, Meyer JP, Krishnan A, Springer SA, Marcus R, Zaller N, Jordan AO, Lincoln T, Flanigan TP, Porterfield J, Altice FL. AIDS Behav. 2013; 17 Suppl 2: 118-127.
HIV and substance use are inextricably intertwined. One-sixth of people living with HIV/AIDS (PLWHA) transition through the correctional system annually. There is paucity of evidence on the impact of substance use disorders on HIV treatment engagement among jail detainees. The authors examined correlates of HIV treatment in the largest sample of PLWHA transitioning through jail in 10 US sites from 2007 to 2011. Cocaine, alcohol, cannabis, and heroin were the most commonly used substances. Drug use severity was negatively and independently correlated with three outcomes just before incarceration: (1) having an HIV care provider (AOR = 0.28; 95 % CI 0.09-0.89); (2) being prescribed antiretroviral therapy (AOR = 0.12; 95 % CI 0.04-0.35) and (3) high levels (>95 %) of antiretroviral medication adherence (AOR = 0.18; 95 % CI 0.05-0.62). Demographic, medical and psychiatric comorbidity, and social factors also contributed to poor outcomes. Evidence-based drug treatments that include multi-faceted interventions, including medication-assisted therapies, are urgently needed to effectively engage this vulnerable population.

Primary Care Patient Characteristics Associated with Completion of 6-Month Buprenorphine Treatment. Neumann AM, Blondell RD, Azadfard M, Nathan G, Homish GG. Addict Behav. 2013; 38(11): 2724-2728.
Opioid addiction is prevalent in the United States. Detoxification followed by behavioral counseling (abstinence-only approach) leads to relapse to opioids in most patients. An alternative approach is substitution therapy with the partial opioid receptor agonist buprenorphine, which is used for opioid maintenance in the primary care setting. This study investigated the patient characteristics associated with completion of 6-month buprenorphine/naloxone treatment in an ambulatory primary care office. A retrospective chart review of 356 patients who received buprenorphine for treatment of opioid addiction was conducted. Patient characteristics were compared among completers and non-completers of 6-month buprenorphine treatment. Of the 356 patients, 127 (35.7%) completed 6-month buprenorphine treatment. Completion of treatment was associated with counseling attendance and having had a past injury. Future research needs to investigate the factors associated with counseling that influenced this improved outcome. Patients with a past injury might suffer from chronic pain, suggesting that buprenorphine might produce analgesia in addition to improving addiction outcome in these patients, rendering them more likely to complete 6-month buprenorphine treatment. Further research is required to test this hypothesis. Combination of behavioral and medical treatment needs to be investigated for primary care patients with opioid addiction and chronic pain.

Offender Diversion into Substance Use Disorder Treatment: The Economic Impact of California's Proposition 36. Anglin MD, Nosyk B, Jaffe A, Urada D, Evans E. Am J Public Health. 2013; 103(6): 1096-1102.
The authors determined the costs and savings attributable to the California Substance Abuse and Crime Prevention Act (SACPA), which mandated probation or continued parole with substance abuse treatment in lieu of incarceration for adult offenders convicted of nonviolent drug offenses and probation and parole violators. The authors used individually linked, population-level administrative data to define intervention and control cohorts of offenders meeting SACPA eligibility criteria. Using multivariate difference-in-differences analysis, they estimated the effect of SACPA implementation on the total and domain-specific costs to state and county governments, controlling for fixed individual and county characteristics and changes in crime at the county level. The additional costs of treatment were more than offset by savings in other domains, primarily in the costs of incarceration. The authors estimated the statewide policy effect as an adjusted savings of $2317 (95% confidence interval = $1905, $2730) per offender over a 30-month post-conviction period. SACPA implementation resulted in greater incremental cost savings for Blacks and Hispanics, who had markedly higher rates of conviction and incarceration. The monetary benefits to government exceeded the additional costs of SACPA implementation and provision of treatment.

Primary Care Provider Cultural Competence and Racial Disparities in HIV Care and Outcomes. Saha S, Korthuis PT, Cohn JA, Sharp VL, Moore RD, Beach MC. J Gen Intern Med. 2013; 28(5): 622-629.
Health professional organizations have advocated for increasing the "cultural competence" (CC) of healthcare providers, to reduce racial and ethnic disparities in patient care. It is unclear whether provider CC is associated with more equitable care. The objective of this study was to evaluate whether provider CC is associated with quality of care and outcomes for patients with HIV/AIDS. This was a survey of 45 providers and 437 patients at four urban HIV clinics in the U.S. Providers' self-rated CC was measured using a novel, 20-item instrument. Outcome measures included patients' receipt of antiretroviral (ARV) therapy, self-efficacy in managing medication regimens, complete 3-day ARV adherence, and viral suppression. Providers' mean age was 44 years; 56 % were women, and 64 % were white. Patients' mean age was 45; 67 % were men, and 77 % were nonwhite. Minority patients whose providers scored in the middle or highest third on self-rated CC were more likely than those with providers in the lowest third to be on ARVs, have high self-efficacy, and report complete ARV adherence. Racial disparities were observed in receipt of ARVs (adjusted OR, 95 % CI for white vs. nonwhite: 6.21, 1.50-25.7), self-efficacy (3.77, 1.24-11.4), and viral suppression (13.0, 3.43-49.0) among patients of low CC providers, but not among patients of moderate and high CC providers (receipt of ARVs: 0.71, 0.32-1.61; self-efficacy: 1.14, 0.59-2.22; viral suppression: 1.20, 0.60-2.42). Provider CC was associated with the quality and equity of HIV care. These findings suggest that enhancing provider CC may reduce racial disparities in healthcare quality and outcomes.

Integrating Buprenorphine Maintenance Therapy into Federally Qualified Health Centers: Real-World Substance Abuse Treatment Outcomes. Haddad MS, Zelenev A, Altice FL. Drug Alcohol Depend. 2013; 131(1-2): 127-135.
Few studies have examined real-world effectiveness of integrated buprenorphine maintenance treatment (BMT) programs in federally qualified health centers (FQHCs). Opioid dependent

patients (N=266) inducted on buprenorphine between July 2007 and December 2008 were retrospectively assessed at Connecticut's largest FQHC network. Six-month BMT retention and opioid-free time were collected longitudinally from electronic health records; 136 (51.1%) of patients were followed for at least 12 months. Participants had a mean age of 40.1 years, were primarily male (69.2%) and treated by family practitioners (70.3%). Co-morbidity included HCV infection (59.8%), mood disorders (71.8%) and concomitant cocaine use (59%). Retention on BMT was 56.8% at 6 months and 61.6% at 12 months for the subset observed over 1 year. Not being retained on BMT at 12 months was associated with cocaine use (AOR=2.18; 95% CI=1.35-3.50) while prescription of psychiatric medication (AOR=0.36; 95% CI 0.20-0.62) and receiving on-site substance abuse counseling (AOR=0.34; 95% CI 0.19, 0.59) improved retention. Two thirds of the participants experienced at least one BMT gap of 2 or more weeks with a mean gap length of 116.4 days. Integrating BMT in this large FQHC network resulted in retention rates similarly reported in clinical trials and emphasizes the need for providing substance abuse counseling and screening for and treating psychiatric comorbidity.

Correlates of HIV Risk Behaviors among Homeless and Unstably Housed Young Adults. Logan JL, Frye A, Pursell HO, Anderson-Nathe M, Scholl JE, Korthuis PT.. Public Health Rep. 2013; 128(3): 153-160.
Homeless young adults are exposed to multiple risk factors for HIV infection. The authors identified HIV risk behaviors and their correlates among homeless young adults in Portland, Oregon. They conducted a community-based, cross-sectional survey of HIV risk behaviors among homeless young adults aged 18-25 years in 2010. Participants completed three study components: (1) an interviewer-administered survey of HIV risk behaviors; (2) a brief, client-centered HIV risk-based counseling session; and (3) rapid HIV testing. Among 208 participants, 45.8% identified as racial/ethnic minority groups, 63.8% were male, and 35.7% self-identified as non-heterosexual. Six participants, all from sexual minority groups, had positive HIV screening results (two newly identified, four previously known) for a seropositivity rate of 2.9%. Female sex, belonging to a sexual minority group, frequent traveling between cities, depression, and alcohol use to intoxication were significantly associated with unprotected sex in univariate analysis. Female sex and high perceived risk of HIV were significantly associated with unprotected sex in multivariate analysis. These findings support the need for enhanced HIV prevention interventions for homeless young adults.

Developing Peerlink To Engage Out-Of-Care HIV+ Substance Users: Training Peers To Deliver A Peer-Led Motivational Intervention with Fidelity. Wolfe H, Haller DL, Benoit E, Bolger KW, Cancienne JC, Ingersoll KS, Sharp V. AIDS Care. 2013; 25(7): 888-894.
Substance use among HIV+ individuals can be a barrier to HIV care, resulting in poor health outcomes. Motivational interviewing (MI) is an effective intervention to reduce substance abuse and increase HIV-related health. Healthcare workers from various backgrounds can be effectively trained in delivering MI interventions; however, there has been limited evidence that peers can effectively deliver MI interventions with fidelity. Peers have traditionally worked in HIV care settings and represent a valid context for a peer-delivered intervention focused on motivational issues. The authors trained four peers in MI. In this paper, they describe the intervention, explain the MI training methods, and investigate whether peers can be trained in MI with fidelity. The MI training included didactic instruction, group workshops, and individual feedback sessions. Two of four peers achieved MI treatment fidelity as measured by the

Motivational Interviewing Treatment Integrity Code Version 3.0. Overall, peers had difficulty using open-ended questions and querying pros and cons, skills thought necessary to elicit change talk. They also tended to give too much direct advice where reflections would have been appropriate. A challenge was training peers to change familiar ways of communicating. Nonetheless, they did well at assessing and highlighting motivation to change. The total training hours (40 h) was long compared with other published MI studies. However, the intervention included several components with two targeted change behaviors. It is likely that peers can be trained in MI with fidelity in less time given a more streamlined intervention. When working with peers who have life stressors similar to the target group, it is important to be flexible in the training.

Impact of Lifetime Alcohol Use On Liver Fibrosis in a Population Of HIV-Infected Patients with and Without Hepatitis C Co-Infection. Fuster D, Tsui JI Cheng DM, Quinn EK, Bridden C, Nunes D, Libman H, Saitz R, Samet JH. Alcohol Clin Exp Res. 2013; 37(9):1527-1535.
The effect of alcohol on liver disease in HIV infection has not been well characterized. The authors performed a cross-sectional multivariable analysis of the association between lifetime alcohol use and liver fibrosis in a longitudinal cohort of HIV-infected patients with alcohol problems. Liver fibrosis was estimated with 2 noninvasive indices, "FIB-4," which includes platelets, liver enzymes, and age; and aspartate aminotrans-ferase/platelet ratio index ("APRI"), which includes platelets and liver enzymes. FIB-4 <1.45 and APRI <0.5 defined the absence of liver fibrosis. FIB-4 >3.25 and APRI >1.5 defined advanced liver fibrosis. The main independent variable was lifetime alcohol consumption (<150 kg, 150 to 600 kg, >600 kg). Subjects (n = 308) were 73% men, mean age 43 years, 49% with hepatitis C virus (HCV) infection, 60% on antiretroviral therapy, 49% with an HIV RNA load <1,000 copies/ml, and 18.7% with a CD4 count <200 cells/mm(3) . Forty-five percent had lifetime alcohol consumption >600 kg, 32.7% 150 to 600 kg, and 22.3% <150 kg; 33% had current heavy alcohol use, and 69% had >9 years of heavy episodic drinking. Sixty-one percent had absence of liver fibrosis and 10% had advanced liver fibrosis based on FIB-4. In logistic regression analyses, controlling for age, gender, HCV infection, and CD4 count, no association was detected between lifetime alcohol consumption and the absence of liver fibrosis (FIB-4 <1.45) (adjusted odds ratio [AOR] = 1.12 [95% CI: 0.25 to 2.52] for 150 to 600 kg vs. <150 kg; AOR = 1.11 [95% CI: 0.52 to 2.36] for >600 kg vs. <150 kg; global p = 0.95). Additionally, no association was detected between lifetime alcohol use and advanced liver fibrosis (FIB-4 >3.25). Results were similar using APRI, and among those with and without HCV infection. In this cohort of HIV-infected patients with alcohol problems, the authors found no significant association between lifetime alcohol consumption and the absence of liver fibrosis or the presence of advanced liver fibrosis, suggesting that alcohol may be less important than other known factors that promote liver fibrosis in this population.

MAPIT: Development of A Web-Based Intervention Targeting Substance Abuse Treatment in the Criminal Justice System. Walters ST, Ondersma SJ, Ingersoll KS, Rodriguez M, Lerch J, Rossheim ME, Taxman FS. J Subst Abuse Treat. 2014 Jan; 46(1):60-65. doi: 10.1016/j.jsat.2013.07.003. Epub 2013 Aug 16.
Although drug and alcohol treatment are common requirements in the U.S. criminal justice system, only a minority of clients actually initiate treatment. This paper describes a two-session, web-based intervention to increase motivation for substance abuse treatment among clients using illicit substances. MAPIT (Motivational Assessment Program to Initiate Treatment) integrates

the extended parallel process model, motivational interviewing, and social cognitive theory. The first session (completed near the start of probation) targets motivation to complete probation, to make changes in substance use (including treatment initiation), and to obtain HIV testing and care. The second session (completed approximately 30 days after session 1) focuses on goal setting, coping strategies, and social support. Both sessions can generate emails or mobile texts to remind clients of their goals. MAPIT uses theory-based algorithms and a text-to-speech engine to deliver custom feedback and suggestions. In an initial test, participants indicated that the program was respectful, easy to use, and would be helpful in making changes in substance use. MAPIT is being tested in a randomized trial in two large U.S. probation agencies. MAPIT addresses the difficulties of many probation agencies to maximize client involvement in treatment, in a way that is cost effective and compatible with the existing service delivery system.

Rapid HIV Testing for Individuals on Probation/Parole: Outcomes of an Intervention Trial. Gordon MS, Kinlock TW, McKenzie M, Wilson ME, Rich JD. AIDS Behav. 2013; 17(6): 2022-2030.

Many probationers and parolees do not receive HIV testing despite being at increased risk for obtaining and transmitting HIV. A two-group randomized controlled trial was conducted between April, 2011 and May, 2012 at probation/parole offices in Baltimore, Maryland and Providence/Pawtucket, Rhode Island. Male and female probationers/parolees were interviewed (n = 1,263) and then offered HIV testing based on random assignment to one of two conditions: (1) On-site rapid HIV testing conducted at the probation/parole office; or (2) Referral for rapid HIV testing off site at a community HIV testing clinic. Outcomes were: (1) undergoing HIV testing; and (2) receipt of HIV testing results. Participants were significantly more likely to be tested on-site at a probation/parole office versus off-site at a HIV testing clinic ($p < 0.001$). There was no difference between the two groups in terms of receiving HIV testing results. Findings indicate that probationers/parolees are willing to be tested on-site and, independent of testing location, are equally willing to receive their results. Implications for expanding rapid HIV testing to more criminal justice related locations and populations are discussed.

A Randomized Clinical Trial of the Health Evaluation and Referral Assistant (HERA): Research Methods. Boudreaux ED, Abar B, Baumann BM, Grissom G. Contemp Clin Trials. 2013; 35(2): 87-96.

The Health Evaluation and Referral Assistant (HERA) is a web-based program designed to facilitate screening, brief intervention, and referral to treatment (SBIRT) for tobacco, alcohol, and drug abuse. After the patient completes a computerized substance abuse assessment, the HERA produces a summary report with evidence-based recommended clinical actions for the healthcare provider (the Healthcare Provider Report) and a report for the patient (the Patient Feedback Report) that provides education regarding the consequences of use, personally tailored motivational messages, and a tailored substance abuse treatment referral list. For those who provide authorization, the HERA faxes the individual's contact information to a substance abuse treatment provider matched to the individual's substance use severity and personal characteristics, like insurance and location of residence (dynamic referral). This paper summarizes the methods used for a randomized controlled trial to evaluate the HERA's efficacy in leading to increased treatment initiation and reduced substance use. The study was performed in four emergency departments. Individual patients were randomized into one of two conditions:

the HERA or assessment only. A total of 4269 patients were screened and 1006 participants enrolled. The sample was comprised of 427 tobacco users, 212 risky alcohol users, and 367 illicit drug users. Forty-two percent used more than one substance class. The enrolled sample was similar to the eligible patient population. The study should enhance understanding of whether computer-facilitated SBIRT can impact process of care variables, such as promoting substance abuse treatment initiation, as well as its effect on subsequent substance abuse and related outcomes.

Days With Pain and Substance Use Disorders: Is There an Association? Edlund MJ, Sullivan MD, Han X, Booth BM. Clin J Pain. 2013; 29(8): 689-695.
The authors investigated possible associations between pain frequency and the 5 most common substance use disorders: alcohol abuse/dependence, cocaine abuse/dependence, methamphetamine abuse/dependence, opioid abuse/dependence, and marijuana abuse/dependence. They used data from the Rural Stimulant Study, a longitudinal (7 waves), observational study of at-risk stimulant users (cocaine and methamphetamine) in Arkansas and Kentucky (n=462). In fixed-effects logistic regression models, the authors regressed their measures of substance use disorders on the number of days with pain in the past 30 days and depression severity. Time periods when individuals had 1 to 15 days [odds ratio (OR)=1.85, P<0.001] or 16+ days (OR=2.18, P<0.001) with pain in the past 30 days were more likely to have a diagnosis of alcohol abuse/dependence, compared with time periods when individuals had no days with pain. Compared with time periods when individuals had no pain days in the past 30 days, time periods when individuals had 16+ pain days were more likely to have a diagnosis of opioid abuse/dependence (OR=3.32, P=0.02). Number of days with pain was not significantly associated with other substance use disorders. Pain frequency seems to be associated with an increased risk for alcohol abuse/dependence and opioid abuse/dependence in this population, and the magnitude of the association is medium to large. Further research is needed to investigate this in more representative populations and to determine causal relationships.

Explaining Long-Term Outcomes among Drug Dependent Mothers Treated in Women-Only Versus Mixed-Gender Programs. Evans E, Li L, Pierce J, Hser Y-I. J Subst Abuse Treat. 2013; 45(3): 293-301.
Specialized substance abuse treatment for parenting women is thought to improve outcomes, but long-term impacts and how they occur are poorly understood. Utilizing a sample of 789 California mothers followed for 10 years after admission to women-only (WO) or mixed-gender (MG) drug treatment, the authors examine the relationship between WO treatment and outcomes and whether it is mediated by post-treatment exposures to criminal justice and health services systems. At follow-up, 48% of mothers had a successful outcome (i.e., no use of illicit drugs, not involved with the criminal justice system, alive). Controlling for patient characteristics, WO (vs. MG) treatment increased the odds of successful outcome by 44%. In the structural equation model WO treatment was associated with fewer post-treatment arrests, which was associated with better outcomes. Women-only substance abuse treatment has long-term benefits for drug-dependent mothers, a relationship that may be partially explained by post-treatment exposure to the criminal justice system. Findings underscore additional leverage points for relapse prevention and recovery-supportive efforts for drug-dependent mothers.

Efficiency of Study Designs in Diagnostic Randomized Clinical Trials. Lu B, Gatsonis C. Stat Med. 2013; 32(9): 1451-1466.
From the patients' management perspective, a good diagnostic test should contribute to both reflecting the true disease status and improving clinical outcomes. The diagnostic randomized clinical trial is designed to combine both diagnostic tests and therapeutic interventions. Evaluation of diagnostic tests is carried out with therapeutic outcomes as the primary endpoint rather than test accuracy. The authors lay out the probability framework for evaluating such trials. They compare two commonly referred designs-the two-arm design and the paired design-in a formal statistical hypothesis testing setup and identify the causal connection between the two tests. The paired design is shown to be more efficient than the two-arm design. The efficiency gains vary depending on the discordant rates of test results. The authors derive sample size formulas for both binary and continuous endpoints. They derive estimation of important quantities under the paired design and also conduct simulation studies to verify the theoretical results. They illustrate the method with an example of designing a randomized study on preoperative staging of bladder cancer.

Perceived Implementation of The Office of Alcoholism and Substance Abuse Services (OASAS) Tobacco-Free Regulation in NY State and Clinical Practice Behaviors to Support Tobacco Cessation: A Repeated Cross-Sectional Study. Eby LTT, Laschober TC. J Subst Abuse Treat. 2013; 45(1): 83-90.
This study measured substance use disorder clinicians' perceptions regarding the implementation extensiveness of the Office of Alcohol and Substance Abuse Services (OASAS) tobacco-free regulation, passed in New York State in July of 2008, at three time-points and across organizations with varying characteristics. Repeated cross-sectional data were collected from clinicians approximately 4 months pre-regulation (time 0, n=362), 10-12 months post-regulation (time 1, n=462), and 20-24 months post-regulation (time 2, n=509). Clinician perceptions of implementation extensiveness (number of required policies in effect), use of tobacco cessation-related intake procedures, and use of guideline recommended counseling for treating tobacco dependence are significantly greater at time 1 and time 2 compared to time 0. Additionally, differences are found in perceived implementation extensiveness based on hospital-based status, profit status, and level of care offered, although the pattern of effects differed some over the three time-points under investigation.

Determinants of Successful Treatment Outcomes among a Sample of Urban American Indians/Alaska Natives: The Role of Social Environments. Spear SE, Crevecoeur-MacPhail D, Denering L, Dickerson D, Brecht M-L. J Behav Health Serv Res. 2013; 40(3): 330-341.
Very few studies have analyzed the role of social environments on substance abuse treatment outcomes among urban American Indians/Alaska Natives (AI/ANs). This study examined a measure of positive treatment response-abstinence from substance use at treatment discharge-among urban AI/ANs in Los Angeles County. The sample included all AI/ANs in outpatient drug-free (e.g., no methadone) treatment and residential treatment from 2004 to 2008 (N = 811). Predictors of abstinence at discharge were (a) having recovery-oriented social support and (b) not having a difficult living situation (i.e., experiencing family conflict and/or living with someone who uses alcohol and/or drugs). Higher levels of recovery-oriented social support in the past 30 days predicted abstinence during outpatient treatment. In residential treatment, retention of 90 days or more, high recovery-oriented social support, and not experiencing difficult living

situations predicted abstinence. Suggestions for optimizing treatment outcomes among AI/ANs and areas of further research are provided.

Unintended Effects of Training On Clinicians' Interest, Confidence, and Commitment in Using Motivational Interviewing. Decker SE, Martino S. Drug Alcohol Depend. 2013; 132(3): 681-687.
Improving clinicians' interest, confidence, and commitment in using evidence-based treatment (EBT) is often an aim of training clinicians in EBT. However, the degree to which these areas actually improve through training and what their relationship is to treatment integrity is unknown. Using data from a multi-site study (Martino et al., 2010) comparing three methods of clinician training in motivational interviewing (MI), changes in interest, confidence, and commitment over time and their relationship to MI adherence and competence were assessed using mixed-effects regression models. Individual patterns of change were examined through cluster analysis. Interest, confidence, and commitment declined over time across training conditions with two distinct patterns: 76% clinicians largely maintained strong interest in MI over time with only slight decreases in confidence and commitment (the "maintainers"), while 24% began with lower initial interest, confidence, and commitment, which subsequently declined over time (the "decliners"). Interest and commitment were not associated with MI adherence and competence; confidence was associated with increased competence in the use of advanced MI strategies. However, decliners demonstrated greater use of MI-inconsistent techniques than maintainers overall (d=0.28).Training in MI may have an unintended consequence of diminishing clinicians' interest, confidence, or commitment in using MI in practice. While attitudinal variables in this study show mixed relationships to MI integrity, they may have some utility in identifying less enthusiastic participants, better preparing them for training, or tailoring training approaches to meet individual training needs.

At a Crossroads: Reentry Challenges and Healthcare Needs among Homeless Female Ex-Offenders. Salem BE, Nyamathi A, Idemundi F, Slaughter R, Ames M. J Forensic Nurs. 2013; 9(1): 14-22.
The exponential increase in the number of women parolees and probationers in the last decade has made women the most rapidly growing group of offenders in the United States. The purpose of this descriptive, qualitative study is to understand the unique gendered experiences of homeless female ex-offenders, in the context of healthcare needs, types of health services sought, and gaps in order to help them achieve a smooth transition post prison release. Focus group qualitative methodology was utilized to engage 14 female ex-offenders enrolled in a residential drug treatment program in Southern California. The findings suggested that for homeless female ex-offenders, there are a myriad of healthcare challenges, knowledge deficits, and barriers to moving forward in life, which necessitates strategies to prevent relapse. These findings support the development of gender-sensitive programs for preventing or reducing drug and alcohol use, recidivism, and sexually transmitted infections among this hard-to-reach population.

Understanding Correlates of Hepatitis C Virus Infection among Homeless Recently Paroled Men. Nyamathi A, Salem BE, Marlow E, Zhang S, Yadav K. J Forensic Nurs. 2013; 9(3): 161-169.
This cross-sectional study assessed predictors of Hepatitis C virus (HCV) positivity with baseline data collected on recently released male parolees (N = 157) participating in a randomized trial

focused on reduction of drug use, recidivism, and risk for hepatitis and HIV infections. In this sample, the prevalence of HCV was 25%. The logistic regression analysis revealed that being an injection drug user was significantly related to HCV infection. However, contrary to most of the current literature, being Black had significantly lower odds of contracting HCV than their White counterparts. Moreover, having lived on the streets, not being part of a close family in childhood, and being older were also associated with HCV infection. These findings highlight the need for skilled assessments that target the vulnerabilities of homeless adults, especially those who have been incarcerated. Understanding drug use patterns, childhood networks, and family relationships, may assist in the design of interventions to reduce risky drug use and address behaviors derived from disadvantaged childhood.

Medicaid Care Management: Description of High-Cost Addictions Treatment Clients.
Neighbors CJ, Sun Y, Yerneni R, Tesiny E, Burke C, Bardsley L, McDonald R, Morgenstern J. J Subst Abuse Treat. 2013; 45(3): 280-286.
High utilizers of alcohol and other drug treatment (AODTx) services are a priority for healthcare cost control. The authors examine characteristics of Medicaid-funded AODTx clients, comparing three groups: individuals <90th percentile of AODTx expenditures (n=41,054); high-cost clients in the top decile of AODTx expenditures (HC; n=5,718); and 1760 enrollees in a chronic care management (CM) program for HC clients implemented in 22 counties in New York State. Medicaid and state AODTx registry databases were combined to draw demographic, clinical, social needs and treatment history data. HC clients accounted for 49% of AODTx costs funded by Medicaid. As expected, HC clients had significant social welfare needs, comorbid medical and psychiatric conditions, and use of inpatient services. The CM program was successful in enrolling some high-needs, high-cost clients but faced barriers to reaching the most costly and disengaged individuals.

Gender Differences in Substance Use Treatment Utilization in The Year Prior to Deployment in Army Service Members. Wooten NR, Mohr BA, Lundgren LM, Adams RS, Merrick EL, Williams TV, Larson MJ. J Subst Abuse Treat. 2013; 45(3): 257-265.
Although military men have heavier drinking patterns, military women experience equal or higher rates of dependence symptoms and similar rates of alcohol-related problems as men at lower levels of consumption. Thus, gender may be important for understanding substance use treatment (SUT) utilization before deployment. Military health system data were analyzed to examine gender differences in both substance use diagnosis (SUDX) and SUT in 152,447 Army service members returning from deployments in FY2010. Propensity score analysis of probability of SUDX indicated that women had lower odds (AOR: 0.91, 95% CI: 0.86-0.96) of military lifetime SUDX. After adjusting for lifetime SUDX using propensity score analysis, multivariate regression found women had substantially lower odds (AOR: 0.61; 95% CI: 0.54-0.70) of using SUT the year prior to deployment. Findings suggest gender disparities in military-provided SUT and a need to consider whether military substance use assessment protocols are sensitive to gender differences.

Hispanics, Incarceration, and TB/HIV Screening: A Missed Opportunity for Prevention.
Gjelsvik A, Chen N, Rich JD. J Immigr Minor Health. 2013; 15(4): 711-717.
Disparities in incarceration rates and in prison-based TB/HIV testing may contribute to health disparities in the communities most affected by incarceration. The authors analyzed Bureau of

Justice Statistics surveys of federal and state prison inmates to assess TB and HIV screening rates for US-born Hispanics, foreign-born Hispanics, non-Hispanic blacks, and non-Hispanic whites. Screening rates were high overall but foreign-born Hispanic inmates had significantly lower odds of being tested for TB in both state (AOR 0.55) and federal prisons (AOR 0.31) compared to white inmates. Foreign-born Hispanics also had lower odds of being tested for HIV in state prisons and Hispanics had lower odds of being tested for HIV in federal prisons compared to white inmates. Screening for infectious diseases in state and federal prisons is high but Hispanics have higher odds of going untested; this has important consequences for prevention of further transmission in the communities to which they return. Dumont DM,

Distress Tolerance and Use of Antiretroviral Therapy among HIV-Infected Individuals in Substance Abuse Treatment. Magidson JF, Seitz-Brown CJ, Listhaus A, Lindberg B, Anderson KE, Daughters SB. AIDS Patient Care STDS. 2013; 27(9): 518-523.
Despite recent clinical guidelines recommending early initiation and widespread use of antiretroviral therapy (ART), many HIV-infected individuals are not receiving ART-in particular low-income, minority substance users. Few studies have examined psychological, as opposed to structural, factors related to not receiving ART in this population. Perceived capacity to tolerate physical and psychological distress, known as distress tolerance (DT), may be a particularly relevant yet understudied factor. The current study tested the relationship between self-reported physical and psychological DT and ART receipt among predominantly low-income, minority HIV-infected substance users (n=77). Psychiatric disorders, biological indicators of health status, ART use, structural barriers to health care, and self-reported physical and psychological DT were assessed. 61% of participants were receiving ART. The only factors that distinguished individuals not on ART were greater avoidance of physical discomfort, higher psychological DT, and higher CD4 count. Both DT measures remained associated with ART use after controlling for CD4 count and were associated with almost a two-fold decrease in likelihood of ART receipt. Current findings suggest higher perceived capacity to tolerate psychological distress and greater avoidance of physical discomfort are important factors associated with lower ART use among substance users and may be important intervention targets.

Using Mobile Phone Technology to Provide Recovery Support for Women Offenders. Scott CK, Johnson K, Dennis ML. Telemed J E Health. 2013; 19(10): 767-771.
Mobile technology holds promise as a recovery tool for people with substance use disorders. However, some populations who may benefit the most may not have access to or experience with mobile phones. Incarcerated women represent a group at high risk for recidivism and relapse to substance abuse. Cost-effective mechanisms must be in place to support their recovery upon release. This study explores using mobile technology as a recovery management tool for women offenders residing in the community following release from jail. This study surveyed 325 minority women offenders with substance use disorders to determine whether or not they use cell phones, their comfort with texting and search features, and the social networks that they access from mobile phones. The authors found that 83% of survey subjects had cell phones; 30% of those were smartphones. Seventy-seven percent of the women reported access to supportive friends, and 88% had close family members they contacted regularly using mobile technology. Results indicated that most of the women were comfortable using a mobile phone, although the majority of them had prepaid minutes rather than plans, and most did currently use smartphones or have the capability to download applications or access social networks via their phones. Most

women reported that they would be comfortable using a mobile phone to text, e-mail, and answer surveys. The high rate of adoption of mobile technology by women offenders makes them a promising target for recovery support delivered via mobile phone.

EMS Runs for Suspected Opioid Overdose: Implications for Surveillance and Prevention. Knowlton A, Weir BW, Hazzard F, Olsen Y, McWilliams J, Fields J, Gaasch W. Prehosp Emerg Care. 2013; 17(3): 317-329.

Opioid (including prescription opiate) abuse and overdose rates in the United States have surged in the past decade. The dearth and limitations of opioid abuse and overdose surveillance systems impede the development of interventions to address this epidemic. The authors explored evidence to support the validity of emergency medical services (EMS) data on naloxone administration as a possible proxy for estimating incidence of opioid overdose. They reviewed data from Baltimore City Fire Department EMS patient records matched with dispatch records over a 13-month time period (2008-2009) based on 2008 Census data. They calculated incidence rates and patient demographic and temporal patterns of naloxone administration, and examined patient evaluation data associated with naloxone administration. Results were compared with the demographic distributions of the EMS patient and city populations and with prior study findings. Of 116,910 EMS incidents during the study period for patients aged 15 years and older, EMS providers administered naloxone 1,297 times (1.1% of incidents), an average of 100 administrations per month. The overall incidence was 1.87 administrations per 1,000 residents per year. Findings indicated that naloxone administration peaked in the summer months (31% of administrations), on weekends (32%), and in the late afternoon (4:00-5:00 pm [8%]); and there was a trend toward peaking in the first week of the month. The incidence of suspected opioid overdose was highest among male patients, white patients, and those in the 45-54-year age group. Findings on temporal patterns were comparable with findings from prior studies. Demographic patterns of suspected opioid overdose were similar to medical examiner reports of demographic patterns of fatal drug- or alcohol-related overdoses in Baltimore in 2008-2009 (88% of which involved opioids). The findings on patient evaluation data suggest some inconsistencies with previously recommended clinical indications of opioid overdose. While these findings suggest limitations of EMS naloxone administration data as a proxy indicator of opioid overdose, the results provide partial support for using these data for estimating opioid overdose incidence and suggest ways to improve such data. The study findings have implications for an EMS role in conducting real-time surveillance and treatment and prevention of opioid abuse and overdose.

Knowledge Management and Informatics Considerations for Comparative Effectiveness Research: A Case-Driven Exploration. Embi PJ, Hebert C, Gordillo G, Kelleher K, Payne PRO. Med Care. 2013; 51 (8 Suppl 3): S38-44.

As clinical data are increasingly collected and stored electronically, their potential use for comparative effectiveness research (CER) grows. Despite this promise, challenges face those wishing to leverage such data. In this paper, the authors aim to enumerate some of the knowledge management and informatics issues common to such data reuse. After reviewing the current state of knowledge regarding biomedical informatics challenges and best practices related to CER, the authors then present 2 research projects at their institution. They analyze these and highlight several common themes and challenges related to the conduct of CER studies. Finally, they represent these emergent themes. The informatics challenges commonly encountered by those

conducting CER studies include issues related to data information and knowledge management (eg, data reuse, data preparation) as well as those related to people and organizational issues (eg, sociotechnical factors and organizational factors). Examples of these are described in further detail and a formal framework for describing these findings is presented. Significant challenges face researchers attempting to use often diverse and heterogeneous datasets for CER. These challenges must be understood in order to be dealt with successfully and can often be overcome with the appropriate use of informatics best practices. Many research and policy questions remain to be answered in order to realize the full potential of the increasingly electronic clinical data available for such research.

Reasons for Misuse of Prescription Medication among Physicians Undergoing Monitoring by a Physician Health Program. Merlo LJ, Singhakant S, Cummings SM, Cottler LB. J Addict Med. 2013; 7(5): 349-353.
Substance-related impairment of physicians is a small but serious problem, with significant consequences for patient safety and public health. The purpose of this study was to identify reasons for prescription drug misuse among physicians referred to a physician health program for monitoring because of substance-related impairment, to develop better mechanisms for prevention and intervention. A total of 55 physicians (94.5% male) who were being monitored by their State physician health program because of substance-related impairment participated in guided focus group discussions. Participation was anonymous. Discussions were transcribed from 9 separate focus groups, lasting 60 to 90 minutes each. Qualitative analyses were conducted to examine themes. All participants were diagnosed with substance dependence, and 69.1% of them endorsed a history of misusing prescription drugs. Participants documented the following 5 primary reasons for prescription drug misuse: (1) to manage physical pain, (2) to manage emotional/psychiatric distress, (3) to manage stressful situations, (4) to serve recreational purposes, and (5) to avoid withdrawal symptoms. The study's results emphasize the importance of self-medication as a leading reason for misusing prescription medications, although recreational use was also an important factor. Prevention efforts targeting prescription drug misuse among physicians should be initiated during medical training, with continuing education requirements throughout the physicians' careers.

Concurrent Life-Course Trajectories of Employment and Marijuana-Use: Exploring Interdependence of Longitudinal Outcomes. Hara M, Huang DYC, Weiss RE, Hser Y-I. J Subst Abuse Treat. 2013; 45(5): 426-432.
This study analyzes data on 7661 individuals who participated in the 1979 National Longitudinal Survey of Youth (NLSY79) to estimate trajectories of employment and marijuana-use over a 17-year period. Bivariate random intercept and slope modeling is applied to examine concurrently the cross-correlation between the two concurrent longitudinal trajectories from age 23 to 39. Parameter estimates indicate baseline level (at age 23) of employment to be negatively correlated with marijuana, suggesting marijuana-use is associated with lower workforce productivity at age 23. The longitudinal employment slope is positively correlated with employment intercept for both males and females, indicating that survey participants with higher levels of employment at age 23 are more likely to have a positive impact on employment trajectory over time. For males, however, the employment slope is also significantly correlated with marijuana intercept (r=-0.07), indicating marijuana-use in early adulthood may uniquely lower workforce productivity over age.

Synergy between Seeking Safety and Twelve-Step Affiliation on Substance Use Outcomes for Women. Morgan-Lopez AA, Saavedra LM, Hien DA, Campbell AN, Wu Elwin, Ruglass L. J Subst Abuse Treat. 2013; 45(2): 179-189.
The Recovery Management paradigm provides a conceptual framework for the examination of joint impact of a focal treatment and post-treatment service utilization on substance abuse treatment outcomes. The authors test this framework by examining the interactive effects of a treatment for comorbid PTSD and substance use, Seeking Safety, and post-treatment Twelve-Step Affiliation (TSA) on alcohol and cocaine use. Data from 353 women in a six-site, randomized controlled effectiveness trial within the NIDA Clinical Trials Network were analyzed under latent class pattern mixture modeling. LCPMM was used to model variation in Seeking Safety by TSA interaction effects on alcohol and cocaine use. Significant reductions in alcohol use among women in Seeking Safety (compared to health education) were observed; women in the Seeking Safety condition who followed up with TSA had the greatest reductions over time in alcohol use. Reductions in cocaine use over time were also observed but did not differ between treatment conditions nor were there interactions with post-treatment TSA. Findings advance understanding of the complexities for treatment and continuing recovery processes for women with PTSD and SUDs, and further support the chronic disease model of addiction.

Longitudinal Missing Data Strategies For Substance Use Clinical Trials Using Generalized Estimating Equations: An Example With A Buprenorphine Trial. McPherson S, Barbosa-Leiker C, McDonell M, Howell D, Roll J. Hum Psychopharmacol. 2013; 28(5): 506-515.
A review of substance use clinical trials indicates that sub-optimal methods are the most commonly used procedures to deal with longitudinal missing information. Listwise deletion (i.e., using complete cases only), positive urine analysis (UA) imputation, and multiple imputation (MI) were used to evaluate the effect of baseline substance use and buprenorphine/naloxone tapering schedule (7 or 28 days) on the probability of a positive UA (UA+) across the 4-week treatment period. The listwise deletion generalized estimating equations (GEE) model demonstrated that those in the 28-day taper group were less likely to submit a UA+ for opioids during the treatment period (odds ratios (OR) = 0.57, 95% confidence interval (CI): 0.39-0.83), as did the positive UA imputation model (OR = 0.43, CI: 0.34-0.55). The MI model also demonstrated a similar effect of taper group (OR = 0.57, CI: 0.42-0.77), but the effect size was more similar to that of the listwise deletion model. Future researchers may find utilization of the MI procedure in conjunction with the common method of GEE analysis as a helpful analytic approach when the missing at random assumption is justifiable.

The Roadmap Relapse Prevention Group Counseling Toolkit: Counselor Adherence and Competence Outcomes. Brooks AC, Carpenedo CM, Fairfax-Columbo J, Clements NT, Benishek LA, Knoblach D, Carise D, Kirby KC. J Subst Abuse Treat. 2013; 45(4): 356-362.
Training counselors in empirically supported treatments (ESTs) far exceeds the ever decreasing resources of community-based treatment agencies. The purpose of this study was to examine outpatient substance abuse group counselors' (n=19) adherence and competence in communicating and utilizing concepts associated with empirically-supported relapse prevention treatment following a brief multimedia toolkit (RoadMAP Toolkit) training. Moderate or large baseline to post-training effect sizes for counselor adherence to toolkit content were identified for 13 of 21 targeted behaviors (overall d range=.06-2.85) with the largest gains on items

measuring active skill practice. Post-training adherence gains were largely maintained at the 6-month follow-up, although no statistically significant improvements were identified over time for counselor competence. This study provides important preliminary support for using a multi-media curriculum approach to increase empirically-supported relapse prevention skills among group counselors. Future research should focus on finding ways to improve counselor skill level and to determine the impact of the Toolkit on client outcomes.

High Rates of Police Detention among Recently Released HIV-Infected Prisoners in Ukraine: Implications for Health Outcomes. Izenberg JM, Bachireddy C, Soule M, Kiriazova T, Dvoryak S, Altice FL. Drug Alcohol Depend. 2013; 133(1): 154-160.
Ukraine's HIV epidemic, primarily affecting people who inject drugs (PWID), is expanding and transitioning despite free opioid substitution therapy (OST) and antiretroviral therapy (ART), two effective ways to reduce HIV transmission. Police detention of PWID not resulting in a formal charge or imprisonment is common, but its prevalence and impact on health are not known. HIV-infected individuals (N=97) released from prison within one year were recruited and surveyed in two HIV-endemic Ukrainian cities about post-release police detention experiences. Data on the frequency of police detention, related adverse events, and impact on OST and ART continuity were collected, and correlates of detention were examined using logistic regression. Detention responses were available for 94 (96.9%) participants, of which 55 (58.5%) reported police detentions (mean=9.4 per person-year). For those detained while prescribed OST (N=28) and ART (N=27), medication interruption was common (67.9% and 70.4%, respectively); 23 of 27 participants prescribed OST (85.2%) were detained en route to/from OST treatment. Significant independent correlates of detention without charges included post-release ART prescription (AOR 4.98, p=0.021), current high-risk injection practices (AOR 5.03, p=0.011), male gender (AOR 10.88, p=0.010), and lower lifetime months of imprisonment (AOR 0.99, p=0.031). HIV-infected individuals recently released from prison in Ukraine experience frequent police detentions, resulting in withdrawal symptoms, confiscation of syringes, and interruptions of essential medications, including ART and OST. Structural changes are urgently needed to reduce police detentions in order to control HIV transmission and improve both individual and public health.

Counseling to Reduce High-Risk Sexual Behavior in HIV Care: A Multi-Center, Direct Observation Study. Flickinger TE, Berry S, Korthuis PT, Saha S, Laws MB, Sharp V, Moore RD, Beach MC. AIDS Patient Care STDS. 2013; 27(7): 416-424.
A key opportunity to reduce HIV transmission lies with healthcare providers counseling HIV-infected patients about safer sex. The authors audio-recorded and transcribed clinical encounters between 45 healthcare providers and 417 of their HIV-infected patients at four outpatient sites in the United States. They used logistic regressions to evaluate associations between patient and provider characteristics, and the occurrence of discussion (any talk about sex) and counseling (advice about safer sex). Of the 417 encounters, discussion of sex occurred in 187 (45% of encounters, 95% CI: 40-50%). Counseling occurred for 49% (95% CI: 35-63%) of patients reporting unsafe sex. Discussion of sex was more likely with younger or less-educated patients and with less cultural difference between patient and provider, while counseling was associated with greater provider mindfulness and lower provider empathy. These findings suggest targets to improve communication regarding sexual risk reduction in HIV care.

Beyond Surveillance: A Role for Respondent-Driven Sampling in Implementation Science. Solomon SS, Lucas GM, Celentano DD, Sifakis F, Mehta SH. Am J Epidemiol. 2013; 178(2): 260-267.
We are now in the fourth decade of the human immunodeficiency virus (HIV) pandemic. Several novel prevention tools have been identified, and prevalence and incidence have declined in many settings. A remaining challenge is the delivery of preventive interventions to hard-to-reach populations, including men who have sex with men and injection drug users. Leaders in the field of HIV have called for a new focus on implementation science, which requires a shift in thinking from individual randomized controlled trials to cluster-randomized trials. Multiple challenges need to be addressed in the conduct of cluster-randomized trials, including: 1) generalizability of the study population to the target population, 2) potential contamination through overlap/ exchange of members of control and intervention clusters, and 3) evaluation of effectiveness at multiple levels of influence. To address these key challenges, the authors propose a novel application of respondent-driven sampling-a chain-referral strategy commonly used for surveillance-in the recruitment of participants for the evaluation of a cluster-randomized trial of a community intervention. They illustrate this application with an empirical example of a cluster-randomized trial that is currently under way to assess the effectiveness of men' wellness centers in improving utilization of HIV counseling and testing among men who have sex with men in India.

Methadone Maintenance Treatment in China: Perceived Challenges from the Perspectives of Service Providers and Patients. Wu F, Peng C-Y, Jiang H, Zhang R, Zhao M, Li J, Hser Y-I. J Public Health (Oxf). 2013; 35(2): 206-212.
China has recently adopted methadone maintenance treatment (MMT) as a national strategy to address the problem of drug abuse and related public health issues such as HIV and HCV infections. However, low enrollment and retention rates suggest that barriers may exist in MMT utilization. This study examined both patients' perceptions and service providers' perceptions of challenges in MMT implementation in China. Four focus groups were conducted in two Chinese cities, Shanghai and Kunming, to explore the perceived and experienced barriers in MMT participation in China. All focus group discussions with participants were audio taped and transcribed. Atlas.ti 5.1 was used to analyze data. Service providers and patient participants reported positive experiences (e.g. effects of MMT in curbing withdrawal symptoms) but also expressed concerns about side effects and continued heroin use during MMT. They also identified barriers in participating and remaining in MMT, including affordability (fee requirement), acceptability (methadone as a substitution, dose, long-term nature), accommodation and accessibility (inconvenient operation hours, lack of transferability to other MMT clinics during travel) and competition between public health and public security. The present findings have implications for reconsidering the current MMT policies and practices in order to improve access, utilization and, ultimately, the effectiveness of MMT in China.

Discrimination, Drugs, and Alcohol among Latina/os in Brooklyn, New York: Differences by Gender. Otiniano Verissimo AD, Gee GC, Iguchi MY, Ford CL, Friedman SR. Int J Drug Policy. 2013; 24(4): 367-373.
Based on a stress-coping framework, the present study investigates the relationship between discrimination and substance use, and the moderating effects of gender. This cross-sectional study analyzes data from Latina/o young adults aged 18-25 (N=401) from Brooklyn, New York.

Multinomial logistic regression was used to test the association between discrimination and substance use. Discrimination was significantly associated with increased odds of substance use adjusting for covariates (e.g. age, education). Gender was a moderator. Discrimination was associated with increased risk of alcohol/cannabis and hard drug use among young Latina women. However, discrimination was associated with decreased risk of alcohol/cannabis use and increased risk of hard drug use among young Latino men. These findings suggest that discrimination is generally associated with risk for substance use, but further that the outcomes vary by gender. Future research should explore gender-specific dimensions of discrimination and their associations with other outcomes.

Factors Associated with Treatment Initiation for Psychiatric and Substance Use Disorders among Persons with HIV. Satre DD, DeLorenze GN, Quesenberry CP, Tsai A, Weisner C. Psychiatr Serv. 2013; 64(8): 745-753.
Prior studies of individuals with HIV infection have found that accessing psychiatric and substance abuse treatment when needed can improve health and prolong life, yet little is known about factors associated with treatment initiation. In a retrospective cohort design including individuals with HIV infection (>14 years old) in an integrated health care system in Northern California, this study included 822 patients with a major psychiatric diagnosis and 1,624 with a substance use disorder diagnosis. Data were extracted from a regional HIV registry and computerized databases. Twenty-four percent (N=198) of study patients with psychiatric diagnoses and 15% (N=245) with substance abuse or dependence received one or more specialty care visits within 12 months of diagnosis. Among patients with a psychiatric diagnosis, significant predictors of visiting a psychiatry clinic included not having an AIDS diagnosis at baseline or before the study (p=.049), having a diagnosis of major depression (p=.013), having a diagnosis of bipolar disorder (p<.001), and receiving a psychiatric diagnosis in 1996 versus later years of the study (p<.01). Among patients with a substance use disorder, significant predictors of initiating substance abuse treatment included age <30 (p=.015) and being in the HIV transmission risk group of injection drug use (p<.001). Clinical, diagnostic, and demographic factors were associated with specialty care treatment initiation in this sample of individuals with HIV infection and substance use or psychiatric disorders. Developing strategies to enhance treatment initiation has the potential to improve outcomes for individuals with HIV infection.

Association between Adolescent Substance Use and Obesity in Young Adulthood: A Group-Based Dual Trajectory Analysis. Huang DYC, Lanza HI, Anglin MD. Addict Behav. 2013; 38(11): 2653-2660.
This study investigated whether and how trajectories of substance use in adolescence were associated with obesity trajectories in young adulthood. The authors hypothesized that: (1) exposure to persistent substance use throughout adolescence may heighten obesity risk in young adulthood; and (2) such associations may differ once gender, ethnicity, socioeconomic status, and obesity status in adolescence, are considered. The study included 5141 adolescents from the child sample of the 1979 National Longitudinal Survey of Youth and utilized biennial data across the 12 assessments (1986-2008) to examine trajectories of substance use behaviors (i.e., cigarette smoking, alcohol use, and marijuana use) from ages 12 to 18 and obesity trajectories from ages 20 to 24. Group-based dual trajectory modeling was applied to examine sequential associations of trajectories of each type of substance use behavior with obesity trajectories. Three distinctive trajectory patterns were respectively identified for cigarette smoking, alcohol use, and marijuana

use from ages 12 to 18, as well as for obesity status (BMI > 30) from ages 20 to 24. Taking into account gender, ethnicity, socioeconomic status, and obesity status in adolescence, adolescents with the most problematic smoking trajectory (High-decreasing) were more likely to exhibit a High-obesity trajectory from ages 20 to 24. Also, adolescents with an Increasing marijuana use trajectory were more likely to exhibit an Increased obesity trajectory in young adulthood. The current study demonstrates that adolescent substance use is associated with subsequent obesity in young adulthood. The associations appear to differ based on the type of substance use and patterns of use.

Feeling Good In Your Own Skin: The Influence of Complimentary Sexual Stereotypes on Risky Sexual Attitudes and Behaviors in a Community Sample of African American Women. Duvall JL, Oser CB, Mooney J, Staton-Tindall M, Havens JR, Leukefeld CG. Women Health. 2013; 53(1): 1-19.

Although negative racial stereotypes may affect the mental and physical health of African Americans, little research has examined the influence of positive or complimentary racial stereotypes on such outcomes. More specifically, this study explored the relationship between African American women's endorsement of complimentary stereotypes about their sexuality and attitudes/behaviors that have been associated with sexual risk. Data were gathered from 206 African American women as part of the Black Women in the Study of Epidemics project. Multivariate regression models were used to examine associations between women's endorsement of complimentary stereotypes about their sexuality and selected sex-related attitudes and behaviors. Participants' endorsement of complimentary sexual stereotypes was significantly positively associated with beliefs that having sex without protection would strengthen their relationship ($B = .28$, $SE = .10$, $p < .01$) and that they could use drugs and always make healthy choices about using protection ($B = .31$, $SE = .09$, $p < .01$). Significant positive associations were also found between complimentary sexual stereotypes and the number of casual sexual partners women reported in the past year ($B = .29$, $SE = .15$, $p = .05$) as well as their willingness to have sex in exchange for money or drugs during that time ($B = .78$, $OR = 2.18$, $p < .05$). These findings suggest that endorsement of complimentary sexual stereotypes by African American women can lead to increased risk behavior, particularly relating to possible infection with HIV or other sexually transmitted infections.

CTN-RELATED RESEARCH

A Randomized Trial of Concurrent Smoking-Cessation and Substance Use Disorder Treatment in Stimulant-Dependent Smokers. Winhusen TM, Brigham GS, Kropp F, Lindblad R, Gardin II JG, Penn P, Hodgkins C, Kelly TM, Douaihy A, McCann M, Love LD, DeGravelles E, Bachrach K, Sonne SC, Hiott B, Haynes L, Sharma G, Lewis DF, VanVeldhuisen P, Theobald J, Ghitza U. J Clin Psychiatry 2013 Dec 10. [Epub ahead of print].

The objective of this study was to evaluate the impact of concurrent treatments for substance use disorder and nicotine-dependence for stimulant-dependent patients. This was a randomized, 10-week trial with follow-up at 3 and 6 months after smoking quit date conducted at 12 substance use disorder treatment programs between February 2010 and July 2012. Adults meeting *DSM-IV-TR* criteria for cocaine and/or methamphetamine dependence and interested in quitting smoking were randomized to treatment as usual (n = 271) or treatment as usual with smoking-cessation treatment (n = 267). All participants received treatment as usual for substance use disorder treatment. Participants assigned to treatment as usual with concurrent smoking-cessation treatment received weekly individual smoking cessation counseling and extended-release bupropion (300 mg/d) during weeks 1–10. During post-quit treatment (weeks 4–10), participants assigned to treatment as usual with smoking-cessation treatment received a nicotine inhaler and contingency management for smoking abstinence. Weekly proportion of stimulant-abstinent participants during the treatment phase, as assessed by urine drug screens and self-report, was the primary outcome. Secondary measures included other substance/nicotine use outcomes and treatment attendance. There were no significant treatment effects on stimulant-use outcomes, as measured by the primary outcome and stimulant-free days, on drug-abstinence, or on attendance. Participants assigned to treatment as usual with smoking-cessation treatment, relative to those assigned to treatment as usual, had significantly better outcomes for drug-free days at 6-month follow-up ($\chi 21 = 4.09$, $P < .05$), with a decrease in drug-free days from baseline of −1.3% in treatment as usual with smoking-cessation treatment and of −7.6% in treatment as usual. Participants receiving treatment as usual with smoking-cessation treatment, relative to those receiving treatment as usual, had significantly better outcomes on smoking point-prevalence abstinence (25.5% vs 2.2%; $\chi 21 = 44.69$, $P < .001$; OR = 18.2). These results suggest that providing smoking-cessation treatment to illicit stimulant-dependent patients in outpatient substance use disorder treatment will not worsen, and may enhance, abstinence from nonnicotine substance use.

A Tale of Two Stimulants: Mentholated Cigarettes May Play a Role in Cocaine, But Not Methamphetamine, Dependence. Winhusen TM, Adinoff B, Lewis DF, Brigham GS, Gardin Ii JG, Sonne SC, Theobald J, Ghitza U. Drug Alcohol Depend. 2013 Sep 11. [Epub ahead of print].

Research suggests that mentholated cigarettes may play a role in cocaine dependence. The purpose of the present study was to expand upon the research on mentholated cigarettes and cocaine dependence and to evaluate the role of mentholated cigarettes in methamphetamine dependence. Secondary analysis of a multisite, randomized trial evaluating the impact of smoking-cessation treatment in stimulant-dependent outpatients (N=538). Participants' reasons for concurrent use of cigarettes and illicit stimulants were assessed via self-report. Stimulant-abstinence was measured by self-report and urine drug screens. Smoking cessation was assessed via self-report and carbon monoxide levels. Of the 301 cocaine-dependent participants, 201

(67%) were menthol and 100 (33%) were non-menthol cigarette smokers. Cocaine-dependent participants who smoked menthol, compared to non-menthol, cigarettes were significantly more likely to report that cigarettes prolong their cocaine high ($X^2(1)=16.3$, $p<.0001$, OR=3.58 [95% CI: 1.88-6.79]) and were less likely to be stimulant abstinent during active treatment (W=3.6, $p<0.001$, d=.39 [95% CI: 0.16-0.62]), at 3-month follow-up ($X^2(1)=14.4$, $p<0.001$, OR=.32 [95% CI: 0.17-0.58]), and at 6-month follow-up ($X^2(1)=4.6$, $p=0.03$, OR=.53 [95% CI: 0.29-0.95]). No parallel differences were found between menthol and non-menthol methamphetamine-dependent smokers. The prevalence of Caucasian menthol smokers was significantly greater in the cocaine-dependent participants (37.2%) than in the methamphetamine-dependent participants (17.61%), ($X^2(1)=14.4$, $p<.001$, OR=2.77 [95% CI:1.62-4.73]). Smoking cessation was not significantly associated with cigarette type for either cocaine- or methamphetamine-dependent participants. The present results suggest that mentholated cigarettes play a role in cocaine, but not methamphetamine, dependence.

Effect of Risk-Reduction Counseling with Rapid HIV Testing on Risk of Acquiring Sexually Transmitted Infections: the AWARE Randomized Clinical Trial. Metsch LR, Feaster DJ, Gooden L, Schackman BR, Matheson T, Das M, Golden MR, Huffaker S, Haynes LF, Tross S, Malotte CK, Douaihy A, Korthuis PT, Duffus WA, Henn S, Bolan R, Philip SS, Castro JG, Castellon PC, McLaughlin G, Mandler RN, Branson B, Colfax GN. JAMA. 2013 Oct 23; 310(16): 1701-1710.

To increase human immunodeficiency virus (HIV) testing rates, many institutions and jurisdictions have revised policies to make the testing process rapid, simple, and routine. A major issue for testing scale-up efforts is the effectiveness of HIV risk-reduction counseling, which has historically been an integral part of the HIV testing process. The objective of this study was to assess the effect of brief patient-centered risk-reduction counseling at the time of a rapid HIV test on the subsequent acquisition of sexually transmitted infections (STIs). From April to December 2010, Project AWARE randomized 5012 patients from 9 sexually transmitted disease (STD) clinics in the United States to receive either brief patient-centered HIV risk-reduction counseling with a rapid HIV test or the rapid HIV test with information only. Participants were assessed for multiple STIs at both baseline and 6-month follow-up. Participants randomized to counseling received individual patient-centered risk-reduction counseling based on an evidence-based model. The core elements included a focus on the patient's specific HIV/STI risk behavior and negotiation of realistic and achievable risk-reduction steps. All participants received a rapid HIV test. The prespecified outcome was a composite end point of cumulative incidence of any of the measured STIs over 6 months. All participants were tested for Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum (syphilis), herpes simplex virus 2, and HIV. Women were also tested for Trichomonas vaginalis. There was no significant difference in 6-month composite STI incidence by study group (adjusted risk ratio, 1.12; 95% CI, 0.94-1.33). There were 250 of 2039 incident cases (12.3%) in the counseling group and 226 of 2032 (11.1%) in the information-only group. Risk-reduction counseling in conjunction with a rapid HIV test did not significantly affect STI acquisition among STD clinic patients, suggesting no added benefit from brief patient-centered risk-reduction counseling.

Genetic Variation in OPRD1 and the Response to Treatment for Opioid Dependence with Buprenorphine in European-American Females. Clarke TK, Crist RC, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. Pharmacogenomics J. 2013 Oct 15. [Epub ahead of print].
Two commonly prescribed treatments for opioid addiction are methadone and buprenorphine. Although these drugs show some efficacy in treating opioid dependence, treatment response varies among individuals. It is likely that genetic factors have a role in determining treatment outcome. This study analyses the pharmacogenetic association of six polymorphisms in OPRD1, the gene encoding the delta-opioid receptor, on treatment outcome in 582 opioid addicted European Americans randomized to either methadone or buprenorphine/naloxone (Suboxone) over the course of a 24-week open-label clinical trial. Treatment outcome was assessed as the number of missed or opioid-positive urine drug screens over the 24 weeks. In the total sample, no single-nucleotide polymorphisms (SNPs) in OPRD1 were significantly associated with treatment outcome in either treatment arm. However, sex-specific analyses revealed two intronic SNPs (rs581111 and rs529520) that predicted treatment outcome in females treated with buprenorphine. Females with the AA or AG genotypes at rs581111 had significantly worse outcomes than those with the GG genotype when treated with buprenorphine (P=0.03, relative risk (RR)=1.67, 95% confidence interval (CI) 1.06-2.1). For rs529520, females with the AA genotype had a significantly worse outcome than those with the CC genotype when (P=0.006, RR=2.15, 95% CI 1.3-2.29). No significant associations were detected in males. These findings suggest that rs581111 and rs52920 may be useful when considering treatment options for female opioid addicts, however, confirmation in an independent sample is warranted.

Treating Nicotine Dependence by Targeting Attention-Deficit/ Hyperactivity Disorder (ADHD) With OROS Methylphenidate: The Role of Baseline ADHD Severity and Treatment Response. Nunes EV, Covey LS, Brigham G, Hu MC, Levin FR, Somoza EC, Winhusen TM. J Clin Psychiatry 2013; 74(10): 983–990.
The objective of this study was to determine whether treatment of attention-deficit/hyperactivity disorder (ADHD) with osmotic-release oral system (OROS) methylphenidate promotes abstinence from smoking among smokers with ADHD who have greater severity of ADHD symptoms at baseline or greater improvement in ADHD during treatment. This is a secondary analysis of data from a randomized, double-blind, 11-week trial conducted between December 2005 and January 2008 at 6 clinical sites; the original trial was sponsored by the National Drug Abuse Clinical Trials Network. Adult cigarette smokers (aged 18–55 years) who met *DSM-IV* criteria for ADHD were randomly assigned to OROS methylphenidate (72 mg/d) (n = 127) or matching placebo (n = 128). All participants received nicotine patches (21 mg/d) and weekly individual smoking cessation counseling. Logistic regression was used to model prolonged abstinence from smoking (ascertained by self-report and breath carbon monoxide testing) as a function of treatment, baseline ADHD Rating Scale-IV (ADHD-RS) score, change in ADHD-RS score during treatment, and their interactions. Treatment interacted with both ADHD-RS score at baseline ($P = .01$) and change in ADHD-RS score during treatment ($P = .008$). Among patients with higher ADHD-RS scores (> 36) at baseline and the most improvement in ADHD during treatment (ADHD-RS change score ≥ 24), 70.0% of those who took OROS methylphenidate achieved abstinence from smoking compared to 36.8% of those who took placebo ($P = .02$). In contrast, among patients with the lowest ADHD-RS baseline scores (≤ 30), 30.3% of those who took OROS methylphenidate achieved abstinence from smoking compared to 60.7% of those

who took placebo (P = .02). OROS methylphenidate, in combination with nicotine patch, may be an effective treatment for nicotine dependence among smokers with more severe ADHD and more robust response of ADHD symptoms to medication. OROS methylphenidate may be counterproductive among smokers with lower severity of ADHD.

Achieving Smoking Abstinence is Associated with Decreased Cocaine Use in Cocaine-Dependent Patients Receiving Smoking-Cessation Treatment. Winhusen TM, Kropp F, Theobald J, Lewis DF. Drug Alcohol Depend. 2013 Sep 27. [Epub ahead of print].
Past research suggests that a significant relationship exists between cigarette smoking and illicit-stimulant abuse. The present study evaluated the association between achieving smoking abstinence in response to smoking-cessation treatment (SCT) and illicit-stimulant abstinence in cocaine- and/or methamphetamine-dependent participants. This was a secondary analysis of a randomized, 10-week trial conducted at 12 substance use disorder (SUD) treatment programs. Two hundred and sixty seven adults, meeting DSM-IV-TR criteria for cocaine and/or methamphetamine-dependence and interested in quitting smoking were randomized to SUD treatment as usual plus SCT consisting of weekly individual smoking cessation counseling, extended-release (XL) bupropion (300mg/day), nicotine inhaler, and contingency management for smoking abstinence. Illicit-stimulant-abstinence was measured by self-report and urine drug screens. Smoking abstinence was assessed via self-report and carbon monoxide levels. A significant effect was found for the cocaine-dependent subsample (N=147) in which participants who stopped smoking were abstinent for illicit stimulants an average of 78.2% of the post-smoking-quit weeks (weeks 4-10) relative to 63.6% in participants who continued smoking ($X^2(1)=8.55$, $p<.01$, $d=0.36$). No significant effects were found for the sample as a whole (N=249) or for the methamphetamine-dependent subsample (N=102). The present results suggest that cocaine-dependent patients achieving smoking abstinence in response to SCT might evidence not only improved smoking outcomes but improved cocaine-use outcomes as well. Future research to replicate this finding appears warranted.

Concurrent Substance Abuse is Associated with Sexual Risk Behavior Among Adults Seeking Treatment for Prescription Opioid Dependence. Meade CS, Bevilacqua LA, Moore ED, Griffin ML, Gardin JG, Potter JS, Hatch-Maillette M, Weiss RD. Am J Addict. 2014 Jan; 23(1): 27-33.
Increasingly, new HIV infections among people who use drugs are attributed to sexual risk behavior. However, HIV prevention research targeting persons with opioid dependence continues to focus on drug injection practices. Moreover, despite the rising prevalence of prescription opioid dependence in the United States, little is known about HIV risk in this population. This study examined the prevalence of sexual risk behavior among patients with opioid dependence who primarily use prescription opioids for non-medical purposes. As part of a multi-site clinical trial, participants (N=653) completed a baseline assessment that included the Risk Behavior Survey. In the past month, 74% were sexually active. Of these, most had opposite sex partners (97.3%) and vaginal intercourse (97.1%); anal intercourse was uncommon (3.1%). The majority reported unprotected intercourse (76.5%), but few had multiple partners (11.3%). Unprotected intercourse was associated with history of other substance dependence (adjusted odds ratio [AOR]=1.73), and having multiple partners was associated with concurrent cocaine use (AOR=2.54). Injection drug use in the past month was rare (2.5%). While the majority of sexually active participants engaged in unprotected intercourse, the proportion with multiple sex

partners was low relative to other samples of persons who use illicit drugs. Among persons with non-medical prescription opioid dependence, those who concurrently use other substances may be at elevated risk for HIV infection. Comprehensive assessment of substance abuse history among individuals dependent upon prescription opioids is critical for identifying patients who may require additional clinical interventions to reduce HIV sexual risk behavior.

Treatment Retention Among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in a Multi-site Trial. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Addiction. 2013 Aug 20. [Epub ahead of print].
The objective of this study was to examine patient and medication characteristics associated with retention and continued illicit opioid use in methadone (MET) versus buprenorphine/naloxone (BUP) treatment for opioid dependence. This secondary analysis included 1,267 opioid-dependent individuals participating in 9 opioid treatment programs between 2006 and 2009 and randomized to receive open-label BUP or MET for 24 weeks. The analyses included measures of patient characteristics at baseline (demographics; use of alcohol, cigarettes, and illicit drugs; self-rated mental and physical health), medication dose and urine drug screens during treatment, and treatment completion and days in treatment during the 24 week trial. The treatment completion rate was 74% for MET vs. 46% for BUP ($p<.01$); the rate among MET participants increased to 80% when the maximum MET dose reached or exceeded 60mg/day. With BUP, the completion rate increased linearly with higher doses, reaching 60% with doses of 30-32mg/day. Of those remaining in treatment, positive opioid urine results were significantly lower (OR=0.63, 95%CI=0.52-0.76, $p<.01$) among BUP relative to MET participants during the first 9 weeks of treatment. Higher medication dose was related to lower opiate use, more so among BUP patients. A Cox proportional hazards model revealed factors associated with dropout: (1) BUP (vs. MET, HR=1.61, CI:1.20-2.15), (2) lower medication dose (<16mg for BUP, <60mg for MET; HR=3.09, CI:2.19-4.37), (3) the interaction of dose and treatment condition (those with higher BUP dose were 1.04 times more likely to drop out than those with lower MET dose, and (4) being younger, Hispanic, and using heroin or other substances during treatment. Provision of methadone appears to be associated with better retention in treatment for opioid dependence than buprenorphine, as does use of provision of higher doses of both medications. Provision of buprenorphine is associated with lower continued use of illicit opioids.

Longitudinal Missing Data Strategies for Substance Use Clinical Trials Using Generalized Estimating Equations: An Example with a Buprenorphine Trial. McPherson S, Barbosa-Leiker C, McDonell M, Howell D, Roll J. Hum Psychopharmacol. 2013 Sep; 28(5): 506-515.
A review of substance use clinical trials indicates that sub-optimal methods are the most commonly used procedures to deal with longitudinal missing information. Listwise deletion (i.e., using complete cases only), positive urine analysis (UA) imputation, and multiple imputation (MI) were used to evaluate the effect of baseline substance use and buprenorphine/naloxone tapering schedule (7 or 28 days) on the probability of a positive UA (UA+) across the 4-week treatment period. The listwise deletion generalized estimating equations (GEE) model demonstrated that those in the 28-day taper group were less likely to submit a UA+ for opioids during the treatment period (odds ratios (OR)=0.57, 95% confidence interval (CI): 0.39-0.83), as did the positive UA imputation model (OR=0.43, CI: 0.34-0.55). The MI model also demonstrated a similar effect of taper group (OR=0.57, CI: 0.42-0.77), but the effect size was

more similar to that of the listwise deletion model. Future researchers may find utilization of the MI procedure in conjunction with the common method of GEE analysis as a helpful analytic approach when the missing at random assumption is justifiable.

Psychometric Properties of the Adjective Rating Scale for Withdrawal Across Treatment Groups, Gender, and Over Time. Barbosa-Leiker C, McPherson S, Mamey MR, Burns GL, Roll J. J Subst Abuse Treat. 2013 Sep 24. [Epub ahead of print].
The Adjective Rating Scale for Withdrawal (ARSW) is commonly used to assess opiate withdrawal in clinical practice and research. The aims of this study were to examine the factor structure of the ARSW, test measurement invariance across gender and treatment groups, and assess longitudinal measurement invariance across the clinical trial. Secondary data analysis of the National Drug Abuse Treatment Clinical Trials Network 000-3, a randomized clinical trial comparing two tapering strategies, was performed. The ARSW was analyzed at baseline, end of taper and 1-month follow-up (N=515 opioid-dependent individuals). A 1-factor model of the ARSW fit the data and demonstrated acceptable reliability. Measurement invariance was supported across gender and taper groups. Longitudinal measurement invariance was not found across the course of the trial, with baseline assessment contributing to the lack of invariance. If change over time is of interest, change from post-treatment through follow-up may offer the most valid comparison.

The Relationship Between Primary Prescription Opioid and Buprenorphine-Naloxone Induction Outcomes in a Prescription Opioid Dependent Sample. Nielsen S, Hillhouse M, Weiss RD, Mooney L, Sharpe Potter J, Lee J, Gourevitch MN, Ling W. Am J Addict. 2013 Sep 24. [Epub ahead of print].
This analysis aims to: (1) compare induction experiences among participants who self-reported using one of the four most commonly reported POs, and (2) examine factors associated with difficult bup-nx induction. The authors' hypothesis, based on previous research and current guidelines, is that those on longer-acting opioids will have experienced more difficult inductions. The Prescription Opioid Addiction Treatment Study (POATS) was a multi-site, randomized clinical trial, using a two-phase adaptive treatment research design. This analysis examines bup-nx induction of participants who self-reported primary PO use of methadone, ER-oxycodone, IR-oxycodone, and hydrocodone (n=569). Analyses examined characteristics associated with difficult induction, defined as increased withdrawal symptoms measured by the Clinical Opiate Withdrawal Scale (COWS) after the first bup-nx dose with higher scores denoting greater withdrawal symptoms/severity. Contrary to the authors' hypothesis, difficult induction experiences did not differ by primary PO type. Those who experienced a post-induction increase in COWS score had lower pre-dose COWS scores compared to those who did not experience a post-induction increase in COWS score (10.09 vs. 12.77, $t(624)=-13.56$, $p<.001$). Demographics characteristics, depression, and pain history did not predict a difficult induction. Difficult bup-nx inductions were not associated with participants' primary PO. Severity of withdrawal, measured with the COWS, was an important variable, reminding clinicians that bup-nx should not be commenced prior to evidence of moderate opioid withdrawal. These findings add to the evidence that with careful procedures, bup-nx can used with few difficulties in PO-dependent patients.

The National Drug Abuse Treatment Clinical Trials Network Data Share Project: Website Design, Usage, Challenges, and Future Directions. Shmueli-Blumberg D, Hu L, Allen C, Frasketi M, Wu LT, Vanveldhuisen P. Clin Trials. 2013 Oct 1. [Epub ahead of print].
There are many benefits of data sharing, including the promotion of new research from effective use of existing data, replication of findings through re-analysis of pooled data files, meta-analysis using individual patient data, and reinforcement of open scientific inquiry. A randomized controlled trial is considered as the 'gold standard' for establishing treatment effectiveness, but clinical trial research is very costly, and sharing data is an opportunity to expand the investment of the clinical trial beyond its original goals at minimal costs. The authors describe the goals, developments, and usage of the Data Share website (http://www.ctndatashare.org) for the National Drug Abuse Treatment Clinical Trials Network (CTN) in the United States, including lessons learned, limitations, and major revisions, and considerations for future directions to improve data sharing. Data management and programming procedures were conducted to produce uniform and Health Insurance Portability and Accountability Act (HIPAA)-compliant de-identified research data files from the completed trials of the CTN for archiving, managing, and sharing on the Data Share website. Since its inception in 2006 and through October 2012, nearly 1700 downloads from 27 clinical trials have been accessed from the Data Share website, with the use increasing over the years. Individuals from 31 countries have downloaded data from the website, and there have been at least 13 publications derived from analyzing data through the public Data Share website. Minimal control over data requests and usage has resulted in little information and lack of control regarding how the data from the website are used. Lack of uniformity in data elements collected across CTN trials has limited cross-study analyses. The Data Share website offers researchers easy access to de-identified data files with the goal to promote additional research and identify new findings from completed CTN studies. To maximize the utility of the website, ongoing collaborative efforts are needed to standardize the core measures used for data collection in the CTN studies with the goal to increase their comparability and to facilitate the ability to pool data files for cross-study analyses.

Family Discord is Associated with Increased Substance Use for Pregnant Substance Users. Denton WH, Adinoff BH, Lewis D, Walker R, Winhusen T. Subst Use Misuse. 2013 Oct 9. [Epub ahead of print].
Childhood abuse and partner violence are associated with prenatal substance abuse, but the potential impact of current family discord, which reflects broader family relationships and encompasses problems less severe than violence, has had little evaluation in pregnant substance users. Using data from 196 pregnant substance users participating in a NIDA Clinical Trials Network randomized clinical trial, the authors examined the relationship of baseline family discord to substance use and treatment session attendance. Family discord was assessed using items from the family composite of the Addiction Severity Index. Substance use was assessed by the Substance Use Calendar and urine drug screens (UDS). Assessments were weekly for four weeks and at two- and four-month post-randomization. Women with family discord were more likely to report living with a problematic substance user, reported a higher percentage of substance use days throughout each study phase, had a greater proportion of positive UDS over the four-month study period, and attended more weeks of treatment during the first month. Specific treatment interventions targeting pregnant women with family discord may be warranted.

Baseline Characteristics and Treatment Outcomes in Prescription Opioid Dependent Patients With and Without Co-occurring Psychiatric Disorder. Griffin ML, Dodd DR, Potter JS, Rice LS, Dickinson W, Sparenborg S, Weiss RD. Am J Drug Alcohol Abuse. 2013 Nov 12. [Epub ahead of print].

Given the growing prevalence of prescription opioid dependence and the considerable rates of additional psychopathology in drug dependence, the authors examined the association between the presence of a co-occurring Axis I psychiatric disorder and sociodemographic and clinical characteristics in this secondary analysis of patients entering a treatment study for dependence on prescription opioids. Treatment outcomes were also compared. Patients dependent on prescription opioids participated in a multi-site, two-phase, randomized, controlled trial to assess different lengths of buprenorphine-naloxone pharmacotherapy and different intensities of counseling (Clinicaltrials.gov identifier: NCT00316277). Among the 653 participants entering the first phase of the trial, 360 entered the second phase, receiving 12 weeks of buprenorphine-naloxone treatment; they are reported here. Half of those participants (180/360) had a current co-occurring psychiatric disorder in addition to substance dependence. Sociodemographic characteristics were similar overall between those with and without a co-occurring psychiatric disorder, but women were 1.6 times more likely than men to have a co-occurring disorder. On several clinical indicators at baseline, participants with a co-occurring disorder had greater impairment. However, they had better opioid use outcomes at the conclusion of 12 weeks of buprenorphine-naloxone stabilization than did participants without a co-occurring disorder. Prescription opioid-dependent patients with a co-occurring psychiatric disorder had a better response to buprenorphine-naloxone treatment despite demonstrating greater impairment at baseline. Additional research is needed to determine the mechanism of this finding and to adapt treatments to address this population.

The Therapeutic Education System: Client and Staff Experiences of Participating in a Randomized Trial of an Online Drug Education System. Abraham S, Vasquez M, Denton D, Walters S, Miele G. Counselor 2013; 14(4): 44-47.

In 2010, an estimated 20.5 million Americans were in need of substance use treatment (Substance Abuse and Mental Health Services Administration, 2011). However, only 1.6 percent actually received any formal treatment, despite the more than 13,000 specialized substance abuse treatment facilities providing outpatient, inpatient and residential care (National Institute on Drug Abuse, 2009). Because of this, researchers and government entities have suggested vastly expanding treatment options to reach more people in need. For people with severe dependency, "treatment" has typically meant face-to-face interactions in a specialized setting. However, recent advances in technology have created opportunities to deliver care across a wider range of substance use severity. Technology has been used to increase treatment accessibility in several ways, both as a stand-alone intervention, and as a way to support and extend face-to-face treatment, particularly for clients who have transportation or scheduling challenges, or must travel from rural areas (Copeland, 2011; Copeland & Martin, 2004; Cucciare, Weingardt & Humphreys, 2009). Automated treatments can also complement existing treatment. For instance, programs can be used to increase treatment initiation or engagement in traditional counseling. At the same time, there may be important challenges in implementing technology-based interventions in community settings, including staff or client resistance (Copeland, 2011). This article describes counselor and client experiences in participating in a clinical research trial of one such program, the Therapeutic Education System (TES). Drawing from the Community

Reinforcement Approach (CRA), TES is an online, self-directed program intended to be integrated early into a clinic's standard treatment. The program was tested in a 10-site project within the National Institute on Drug Abuse's (NIDA) Treatment Clinical Trials Network (CTN). Outpatient clients were recruited early in their treatment sequence (see Campbell et al., 2012, for a full description of study design and methods). Participants were randomly assigned to standard outpatient care, which generally consists of two to three, two-hour group meetings per week, or to outpatient care plus TES. TES participants replaced an equivalent amount of group therapy with time spent on TES, completing at least four modules per week for 12 weeks. Passing the module exam and negative drug screens were rewarded with chances to draw prizes from a computer-animated "fish bowl." They stated that clients who completed TES appeared to be more motivated in treatment, shared new insights and asked advanced questions. Counselors also noted that TES clients reported increased self-esteem related to increased computer literacy and awareness of others who were dealing with similar struggles. The final analyses of the acceptability and usefulness of TES are forthcoming, but the program, which was well tolerated by staff and clients alike, may help improve the delivery of recovery-oriented life-skills materials by rural treatment providers, as well as for isolated or transportation-challenged individuals. As technology is further integrated into mainstream treatment, counselors are encouraged to make resources like TES available to clients (SAMHSA, 2012).

WOMEN & SEX/GENDER DIFFERENCES-RELATED RESEARCH

Gender Differences in Emotion Expression in Children: A Meta-analytic Review. Chaplin TM, Aldao A. Psychol Bull. 2013 Jul; 139(4): 735-765.
Emotion expression is an important feature of healthy child development that has been found to show gender differences. However, there has been no empirical review of the literature on gender and facial, vocal, and behavioral expressions of different types of emotions in children. The present study constitutes a comprehensive meta-analytic review of gender differences and moderators of differences in emotion expression from infancy through adolescence. The authors analyzed 555 effect sizes from 166 studies with a total of 21,709 participants. Significant but very small gender differences were found overall, with girls showing more positive emotions (g = -.08) and internalizing emotions (e.g., sadness, anxiety, sympathy; g = -.10) than boys, and boys showing more externalizing emotions (e.g., anger; g = .09) than girls. Notably, gender differences were moderated by age, interpersonal context, and task valence, underscoring the importance of contextual factors in gender differences. Gender differences in positive emotions were more pronounced with increasing age, with girls showing more positive emotions than boys in middle childhood (g = -.20) and adolescence (g = -.28). Boys showed more externalizing emotions than girls at toddler/preschool age (g = .17) and middle childhood (g = .13) and fewer externalizing emotions than girls in adolescence (g = -.27). Gender differences were less pronounced with parents and were more pronounced with unfamiliar adults (for positive emotions) and with peers/when alone (for externalizing emotions). These findings of gender differences in emotion expression in specific contexts have important implications for gender differences in children's healthy and maladaptive development.

Central Nervous System Effects of Prenatal Selective Serotonin Reuptake Inhibitors: Sensing the Signal through the Noise. Gur TL, Kim DR, Epperson CN. Psychopharmacology (Berl). 2013 Jun; 227(4): 567-582.
Women are increasingly prescribed selective serotonin reuptake inhibitors (SSRIs) during pregnancy, with potential implications for neurodevelopment. Whether prenatal SSRI exposure has an effect on neurodevelopment and behavior in the offspring is an important area of investigation. The aim of this paper was to review the existing preclinical and clinical literature of prenatal SSRI exposure on serotonin-related behaviors and markers in the offspring. The goal is to determine if there is a signal in the literature that could guide clinical care and/or inform research. Preclinical studies (n=4) showed SSRI exposure during development enhanced depression-like behavior. Half of rodent studies examining anxiety-like behavior (n=13) noted adverse effects with SSRI exposure. A majority of studies of social behavior (n=4) noted a decrease in sociability in SSRI exposed offspring. Human studies (n=4) examining anxiety in the offspring showed no adverse effects of prenatal SSRI exposure. The outcome of one study suggested that children with autism were more likely to have a mother who was prescribed an SSRI during pregnancy. Preclinical findings in rodents exposed to SSRIs during development point to an increase in depression- and anxiety-like behavior and alteration in social behaviors in the offspring, though both the methods used and the findings were not uniform. These data are not robust enough to discourage use of SSRIs during human pregnancy, particularly given the known adverse effects of maternal mental illness on pregnancy outcomes and infant neurodevelopment. Future research should focus on consistent animal models and prospective human studies with larger samples.

Cerebral Gray Matter Volumes and Low-Frequency Fluctuation of BOLD Signals in Cocaine Dependence: Duration of Use and Gender Difference. Ide JS, Zhang S, Hu S, Sinha R, Mazure CM, Li CS. Drug and Alcohol Dependence. 2013 Sep 17. [Epub ahead of print].
Magnetic resonance imaging has provided a wealth of information on altered brain activations and structures in individuals addicted to cocaine. However, few studies have considered the influence of age and alcohol use on these changes. The authors examined gray matter volume with voxel based morphometry (VBM) and low frequency fluctuation (LFF) of BOLD signals as a measure of cerebral activity of 84 cocaine dependent (CD) and 86 healthy control (HC) subjects. They performed a covariance analysis to account for the effects of age and years of alcohol use. Compared to HC, CD individuals showed decreased gray matter (GM) volumes in frontal and temporal cortices, middle/posterior cingulate cortex, and the cerebellum, at $p<0.05$, corrected for multiple comparisons. The GM volume of the bilateral superior frontal gyri (SFG) and cingulate cortices were negatively correlated with years of cocaine use, with women showing a steeper loss in the right SFG in association with duration of use. In contrast, the right ventral putamen showed increased GM volume in CD as compared to HC individuals. Compared to HC, CD individuals showed increased fractional amplitude of LFF (fALFF) in the thalamus, with no significant overlap with regions showing GM volume loss. These results suggested that chronic cocaine use is associated with distinct changes in cerebral structure and activity that can be captured by GM volume and fALFF of BOLD signals.

Smoking Topography and Abstinence in Adult Female Smokers. McClure EA, Saladin ME, Baker NL, Carpenter MJ, Gray KM. Addict Behav. 2013 Dec; 38(12): 2833-2836.
Preliminary evidence, within both adults and adolescents, suggests that the intensity with which cigarettes are smoked (i.e., smoking topography) is predictive of success during a cessation attempt. These reports have also shown topography to be superior compared to other variables, such as cigarettes per day, in the prediction of abstinence. The possibility that gender may influence this predictive relationship has not been evaluated but may be clinically useful in tailoring gender-specific interventions. Within the context of a clinical trial for smoking cessation among women, adult daily smokers completed a laboratory session that included a 1-hour ad libitum smoking period in which measures of topography were collected (N=135). Participants were then randomized to active medication (nicotine patch vs. varenicline) and abstinence was monitored for 4 weeks. Among all smoking topography measures and all abstinence outcomes, a moderate association was found between longer puff duration and greater puff volume and continued smoking during the active 4-week treatment phase, but only within the nicotine patch group. Based on the weak topography-abstinence relationship among female smokers found in the current study, future studies should focus on explicit gender comparisons to examine if these associations are specific to or more robust in male smokers.

Prenatal Cocaine Exposure and Gray Matter Volume in Adolescent Boys and Girls: Relationship to Substance Use Initiation. Rando K, Chaplin TM, Potenza MN, Mayes L, Sinha R. Biol Psychiatry. 2013 Oct 1; 74(7): 482-489.
Studies of prenatal cocaine exposure have primarily examined childhood populations. Studying adolescents is especially important because adolescence is a time of changing motivations and initiation of substance use. Using magnetic resonance imaging and whole-brain voxel-based morphometry, PI assessed gray matter volume (GMV) differences in 42 prenatally cocaine exposed (PCE) and 21 noncocaine-exposed (NCE) adolescents, aged 14 to 17 years.

Associations between GMV differences in significant clusters and the probability of substance use initiation were examined. PCE relative to NCE adolescents demonstrated three clusters of lower GMV involving a limbic and paralimbic ($p < .001$, family-wise error [FWE] corrected), superior frontal gyrus ($p = .001$, FWE corrected), and precuneus ($p = .019$, FWE corrected) cluster. GMVs in the superior frontal and precuneus clusters were associated with initiation of substance use. Each 1-mL decrease in GMV increased the probability of initiating substance use by 69.6% ($p = .01$) in the superior frontal cluster and 83.6% ($p = .02$) in the precuneus cluster. PCE is associated with structural differences in cortical and limbic regions. Lower GMVs in frontal cortical and posterior regions are associated with substance use initiation and may represent biological risk markers for substance use.

Sex Differences in Impulsive Action and Impulsive Choice. Weafer J, de Wit H. Addict Behav. 2013 Nov 6 [Epub ahead of print].
Here, the authors review the evidence for sex differences in behavioral measures of impulsivity for both humans and laboratory animals. They focus on two specific components of impulsivity: impulsive action (i.e., difficulty inhibiting a prepotent response) and impulsive choice (i.e., difficulty delaying gratification). Sex differences appear to exist on these measures, but the direction and magnitude of the differences vary. In laboratory animals, impulsive action is typically greater in males than females, whereas impulsive choice is typically greater in females. In humans, women discount more steeply than men, but sex differences on measures of impulsive action depend on tasks and subject samples. The authors discuss implications of these findings as they relate to drug addiction. They also point out the major gaps in this research to date, including the lack of studies designed specifically to examine sex differences in behavioral impulsivity, and the lack of consideration of menstrual or estrous phase or sex hormone levels in the studies.

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Research Branch

Medicinal Chemistry Section

A Single Glycine In Extracellular Loop 1 Interconverts the Pharmacological Specificity of Dopamine D2 and D3 Receptors. Michino M, Donthamsetti P, Beuming T, Banala, AK, Duan L, Roux T, Han Y, Trinquet E, Newman AH, Javitch JA, Shi L Mol Pharmacol 2013; 84(6): 854-864.

Subtype-selective agents for the dopamine D3 receptor (D3R) have been considered as potential medications for drug addiction and other neuropsychiatric disorders. Medicinal chemistry efforts have led to the discovery of 4-phenylpiperazine derivatives that are >100-fold selective for the dopamine D3 receptor over dopamine D2 receptor (D2R), despite high sequence identity (78% in the transmembrane domain). Based on the recent crystal structure of D3R, the authors demonstrated that the 4-phenylpiperazine moiety in this class of D3R-selective compounds binds to the conserved orthosteric binding site, whereas the extended aryl amide moiety is oriented toward a divergent secondary binding pocket (SBP). In an effort to further characterize molecular determinants of the selectivity of these compounds, the authors modeled their binding modes in D3R and D2R by comparative ligand docking and molecular dynamics simulations. They found that the aryl amide moiety in the SBP differentially induces conformational changes in transmembrane segment 2 and extracellular loop 1 (EL1), which amplify the divergence of the SBP in D3R and D2R. Receptor chimera and site-directed mutagenesis studies were used to validate these binding modes and to identify a divergent glycine in EL1 as critical to D3R over D2R subtype selectivity. A better understanding of drug-dependent receptor conformations such as these is key to the rational design of compounds targeting a specific receptor among closely related homologs, and may also lead to discovery of novel chemotypes that exploit subtle differences in protein conformations.

A Novel mGluR5 Antagonist, MFZ 10-7, Inhibits Cocaine-Taking and Cocaine-Seeking Behavior In Rats. Keck TM, Zou MF, Bi GH, Zhang HY, Wang XF, Yang HJ, Srivastava R, Gardner EL, Xi ZX, Newman AH. Addiction Biol 2013; e-pub Sept. 4, 2103.

Preclinical studies suggest that negative allosteric modulators (NAMs) of the metabotropic glutamate receptor subtype 5 (mGluR5), including MPEP (2-methyl-6-(phenylethynyl)pyridine), MTEP (3-((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine) and fenobam, are highly effective in attenuating drug-taking and drug-seeking behaviors. However, both MPEP and MTEP have no translational potential for use in humans due to their off-target effects and short half-lives. Here, the authors report that MFZ 10-7 (3-fluoro-5-((6-methylpyridin-2-yl)ethynyl)benzonitrile), a novel mGluR5 NAM, is more potent and selective than MPEP, MTEP and fenobam in both in vitro binding and functional assays. Similar to MTEP, intraperitoneal administration of MFZ 10-7 inhibited intravenous cocaine self-administration, cocaine-induced reinstatement of drug-seeking behavior and cocaine-associated cue-induced cocaine-seeking behavior in rats. Although MFZ 10-7 and MTEP lowered the rate of oral sucrose self-administration, they did not alter total sucrose intake. Further, MFZ 10-7 appeared to be more potent than MTEP in inducing downward shifts in the cocaine dose-response curve, but less effective than MTEP in attenuating sucrose-induced reinstatement of sucrose-seeking behavior. MFZ 10-7 and MTEP had no effect

on basal locomotor behavior. These findings not only provide additional evidence supporting an important role for mGluR5 in cocaine reward and addiction, but also introduce a new tool for both in vitro and in vivo investigations with which to further characterize this role.

Feeding Condition and the Relative Contribution of Different Dopamine Receptor Subtypes to the Discriminative Stimulus Effects of Cocaine in Rats. Baladi M, Newman AH, France CP. Psychopharmacology 2013; e-pub Sept. 13, 2013.
The contribution of dopamine receptor subtypes in mediating the discriminative stimulus effects of cocaine is not fully established. Many drug discrimination studies use food to maintain responding, necessitating food restriction, which can alter drug effects. This study established stimulus control with cocaine (10 mg/kg) in free-feeding and food-restricted rats responding under a schedule of stimulus shock termination (SST) and in food-restricted rats responding under a schedule of food presentation to examine whether feeding condition or the reinforcer used to maintain responding impacts the effects of cocaine. Dopamine receptor agonists and antagonists were examined for their ability to mimic or attenuate, respectively, the effects of cocaine. Apomorphine, quinpirole, and lisuride occasioned >90 % responding on the cocaine-associated lever in free feeding rats responding under a schedule of SST; apomorphine, but not quinpirole or lisuride, occasioned >90 % responding on the cocaine lever in food-restricted rats responding under a schedule of SST. In food-restricted rats responding for food these drugs occasioned little cocaine lever responding and were comparatively more potent in decreasing responding. In free-feeding rats, the effects of cocaine were attenuated by the D2/D3 receptor antagonist raclopride and the D3 receptor-selective antagonist PG01037. In food-restricted rats, raclopride and the D2 receptor-selective antagonist L- 741,626 attenuated the effects of cocaine. Raclopride antagonized quinpirole in all groups while PG01037 antagonized quinpirole only in free-feeding rats. These results demonstrate significant differences in the discriminative stimulus of cocaine that are due to feeding conditions and not to the use of different reinforcers across procedures.

Design and Synthesis of Citalopram Analogues As Novel Probes For the Serotonin Transporter S1 and S2 Binding Sites. Banala AK, Zhang P, Plenge P, Cyriac G, Kopajtic T, Katz JL, Loland CJ, Newman AH. J Med Chem 2013; e-pub Nov. 15, 2013.
The serotonin transporter (SERT) is the primary target for antidepressant drugs. The existence of a high affinity primary orthosteric binding site (S1) and a low affinity secondary site (S2) has been described and their relation to antidepressant pharmacology has been debated. Herein, structural modifications to the N-, 4, 5, and 4'-positions of (±)citalopram are reported. All of the analogues were SERT-selective and demonstrated that steric bulk was tolerated at the SERT S1 site, including two dimeric ligands. In addition, 8 analogues were identified with similar potencies to S-citalopram for decreasing the dissociation of [3H]S-citalopram from the S1 site, via allosteric modulation at S2. Both dimeric compounds had similar affinities for the SERT S1 site (Ki=19.7 and 30.2 nM, respectively), whereas only the N-substituted analogue was as effective as S-citalopram in allosterically modulating the binding of [3H]S-citalopram via the S2 site.

Modafinil: A Potential Enhancer of Cognitive Performance and a Treatment for Substance Use Disorders. Mereu M, Bonci A, Newman AH, Tanda G. Psychopharmacology – Special Waletsky Issue, 2013; 229(3): 415-434.

Modafinil (MOD) and its R-enantiomer (R-MOD) are approved medications for narcolepsy and other sleep disorders. They have also been used, off-label, as cognitive enhancers in populations of patients with mental disorders, including substance abusers that demonstrate impaired cognitive function. A debated nonmedical use of MOD in healthy individuals to improve intellectual performance is raising questions about its potential abuse liability in this population. MOD has low micromolar affinity for the dopamine transporter (DAT). Inhibition of dopamine (DA) reuptake via the DAT explains the enhancement of DA levels in several brain areas, an effect shared with psychostimulants like cocaine, methylphenidate, and the amphetamines. However, its neurochemical effects and anatomical pattern of brain area activation differ from typical psychostimulants and are consistent with its beneficial effects on cognitive performance processes such as attention, learning, and memory. At variance with typical psychostimulants, MOD shows very low, if any, abuse liability, in spite of its use as a cognitive enhancer by otherwise healthy individuals. Finally, recent clinical studies have focused on the potential use of MOD as a medication for treatment of drug abuse, but have not shown consistent outcomes. However, positive trends in several result measures suggest that medications that improve cognitive function, like MOD or R-MOD, may be beneficial for the treatment of substance use disorders in certain patient populations.

Psychobiology Section, Molecular Targets and Medications Discovery Branch

Stimulants as Specific Inducers of Dopamine-Independent Sigma Agonist Self-Administration In Rats. Hiranita T, Soto PL, Tanda G, Kopajtic TA, Katz JL. Journal of Pharmacology and Experimental Therapeutics 2013; 347: 20-29.

A previous study showed that cocaine self-administration induced dopamine-independent reinforcing effects of sigma agonists mediated by their selective actions at sigma1 receptors (σ1Rs), which are intracellularly-mobile chaperone proteins implicated in abuse-related effects of stimulants. The present study assessed whether the induction was specific to self-administration of cocaine. Rats were trained to self-administer the dopamine releaser, d-methamphetamine (0.01-0.32 mg/kg/injection), the mu-opioid receptor agonist, heroin (0.001-0.032 mg/kg/injection), and the non-competitive N-methyl-D-aspartate (NMDA) receptor/channel antagonist ketamine (0.032-1.0 mg/kg/injection). As with cocaine, self-administration of d-methamphetamine induced reinforcing effects of the selective σ1R agonists, PRE-084 and (+)-pentazocine (0.032-1.0 mg/kg/injection, each). In contrast, neither self-administration of heroin nor ketamine induced PRE-084 or (+)-pentazocine (0.032-10 mg/kg/injection, each) self-administration. Though the σ1R agonists did not maintain responding in subjects with histories of heroin or ketamine self-administration, substitution for those drugs was obtained with appropriate agonists (e.g. remifentanil, 0.1-3.2 μg/kg/injection, for heroin and (+)-MK 801, 0.32-10.0 μg/kg/injection, for ketamine). The σR antagonist BD 1008 (1.0-10 mg/kg) dose-dependently blocked PRE-084 self-administration but was inactive against d-methamphetamine, heroin, and ketamine. In contrast, PRE-084 self-administration was affected neither by the dopamine receptor antagonist, (+)-butaclamol (10-100 μg/kg), nor the opioid antagonist, (-)-naltrexone (1.0-10 mg/kg), whereas these antagonists were active against

d-methamphetamine and heroin self-administration, respectively. The results indicate that experience specifically with indirect-acting dopamine agonists induces reinforcing effects of previously inactive σ1R agonists. It is further suggested that induced σ1R reinforcing mechanisms may play an essential role in treatment-resistant stimulant abuse, suggesting new approaches for the development of effective medications for its treatment.

Office of the Scientific Director

Synaptic Plasticity Section

Neural Estimates of Imagined Outcomes in the Orbitofrontral Cortex Drive Behavior and Learning. Takahashi YK, Chang CY, Lucantonio F, Haney RZ, Berg BA, Bonci A, Schoenbaum G. Neuron 2013; 80: 507-518.
Imagination, defined as the ability to interpret reality in ways that diverge from past experience, is fundamental to adaptive behavior. This can be seen at a simple level in our capacity to predict novel outcomes in new situations. The ability to anticipate outcomes never before received can also influence learning if those imagined outcomes are not received. The orbitofrontal cortex is a key candidate for where the process of imagining likely outcomes occurs; however, its precise role in generating these estimates and applying them to learning remain open questions. Here the authors address these questions by showing that single-unit activity in the orbitofrontal cortex reflects novel outcome estimates. The strength of these neural correlates predicted both behavior and learning, learning that was abolished by temporally specific inhibition of orbitofrontal neurons. These results are consistent with the proposal that the orbitofrontal cortex is critical for integrating information to imagine future outcomes.

Methamphetamine Downregulates Striatal Glutamate Receptors Via Diverse Epigenetic Mechanisms. Jayanthi S, McCoy MT, Chen B, Britt JP, Kourrich S, Yau HJ, Ladenheim B, Krasnova IN, Bonci A, Cadet JL. Biol Psychiatry 2013; e-pub October 16, 2013.
Chronic methamphetamine (METH) exposure causes neuroadaptations at glutamatergic synapses. To identify the METH-induced epigenetic underpinnings of these neuroadaptations, the authors injected increasing METH doses to rats for 2 weeks and measured striatal glutamate receptor expression. They then quantified the effects of METH exposure on histone acetylation. They also measured METH-induced changes in DNA methylation and DNA hydroxyl-methylation. Chronic METH decreased transcript and protein expression of GluA1 and GluA2 alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and GluN1 N-methyl-D-aspartate receptor subunits. These changes were associated with altered electrophysiological glutamatergic responses in striatal neurons. Chromatin immunoprecipitation-polymerase chain reaction revealed that METH decreased enrichment of acetylated histone H4 on GluA1, GluA2, and GluN1 promoters. Methamphetamine exposure also increased repressor element-1 silencing transcription factor (REST) corepressor 1, methylated CpG binding protein 2, and histone deacetylase 2 enrichment, but not of sirtuin 1 or sirtuin 2, onto GluA1 and GluA2 gene sequences. Moreover, METH caused interactions of REST corepressor 1 and methylated CpG binding protein 2 with histone deacetylase 2 and of REST with histone deacetylase 1. Surprisingly, methylated DNA immunoprecipitation and hydroxymethylated DNA immunoprecipitation-polymerase chain reaction revealed METH-

induced decreased enrichment of 5-methylcytosine and 5-hydroxymethylcytosine at GluA1 and GluA2 promoter sequences. Importantly, the histone deacetylase inhibitor, valproic acid, blocked METH-induced decreased expression of AMPAR and N-methyl-D-aspartate receptor subunits. Finally, valproic acid also attenuated METH-induced decrease H4K16Ac recruitment on AMPAR gene sequences. These observations suggest that histone H4 hypoacetylation may be the main determinant of METH-induced decreased striatal glutamate receptor expression.

Binge Ethanol-Drinking Potentiates Corticotropin Releasing Factor R1 Receptor Activity In the Ventral Tegmental Area. Sparta DR, Hopf FW, Gibbs SL, Cho SL, Stuber GD, Messing RO, Ron D, Bonci A. Alcohol Clin Exp Res. 2013; e-pub June 13, 2013**.** Corticotropin releasing factor (CRF) and urocortin play an important role in many stress responses and also can regulate ethanol (EtOH) intake. Adaptations in CRF signaling in the central amygdala promote EtOH consumption after long-term EtOH intake in dependent animals and also after brief periods of binge EtOH intake. Thus, even brief episodes of EtOH consumption can alter the function of the CRF system, allowing CRF to regulate EtOH intake. Here, the authors examined whether brief binge EtOH consumption leads to CRF receptor adaptations within the ventral tegmental area (VTA), a structure involved in signaling rewarding and aversive events and important in the development and expression of drug and alcohol addiction. They utilized a mouse model of binge drinking known as drinking in the dark (DID), where C57BL/6J mice drink approximately 6 g/kg in 4 hours and achieve blood EtOH concentrations of approximately 100 mg/dl, which is equivalent to binge drinking in humans. The authors used ex vivo whole-cell recordings from putative VTA dopamine (DA) neurons to examine CRF regulation of NMDA receptor (NMDAR) currents. They also examined the impact of CRF receptor antagonist injection in the VTA on binge EtOH intake. Ex vivo whole-cell recordings from putative VTA DA neurons showed enhanced CRF-mediated potentiation of NMDAR currents in juvenile mice that consumed EtOH in the DID procedure. CRF-induced potentiation of NMDAR currents in EtOH-drinking mice was blocked by administration of CP-154,526 (3 μM), a selective CRF1 receptor antagonist. Furthermore, intra-VTA infusion of CP-154,526 (1 μg) significantly reduced binge EtOH consumption in adult mice. These results were not due to alterations of VTA NMDAR number or function, suggesting that binge drinking may enhance signaling through VTA CRF1 receptors onto NMDARs. The authors conclude that altered CRF1 receptor-mediated signaling in the VTA promotes binge-like EtOH consumption in mice, which supports the idea that CRF1 receptors may therefore be a promising pharmacological target for reducing binge drinking in humans.

PTEN Knockdown Alters Dendritic Spine/Protrusion Morphology, Not Density. Haws ME, Jaramillo TC, Espinosa-Becerra F, Widman A, Stuber GD, Sparta DR, Tye KM, Russo SJ, Parada LF, Kaplitt M, Bonci A, Powell CM J Comp Neurol. 2013, e-pub November 21, 2013. Mutations in phosphatase and tensin homolog deleted on chromosome ten (PTEN) are implicated in neuropsychiatric disorders including autism. Previous studies report that PTEN knockdown in neurons in vivo leads to increased spine density and synaptic activity. To better characterize synaptic changes in neurons lacking PTEN, the authors examined the effects of shRNA knockdown of PTEN in basolateral amygdala neurons on synaptic spine density and morphology using fluorescent dye confocal imaging. Contrary to previous studies in dentate gyrus, they find that knockdown of PTEN in basolateral amygdala leads to a significant decrease in total spine density in distal dendrites. Curiously, this decreased spine density is associated with increased

miniature excitatory post-synaptic current frequency and amplitude, suggesting an increase in number and function of mature spines. These seemingly contradictory findings were reconciled by spine morphology analysis demonstrating increased mushroom spine density and size with correspondingly decreased thin protrusion density at more distal segments. The same analysis of PTEN conditional deletion in dentate gyrus demonstrated that loss of PTEN does not significantly alter total density of dendritic protrusions in the dentate gyrus, but does decrease thin protrusion density and increases density of more mature mushroom spines. These findings suggest that, contrary to previous reports, PTEN knockdown may not induce de novo spinogenesis, but instead may increase synaptic activity by inducing morphological and functional maturation of spines. Furthermore, behavioral analysis of basolateral amygdala PTEN knockdown suggests that these changes limited only to the basolateral amygdala complex may not be sufficient to induce increased anxiety-related behaviors.

Clinical Pharmacology and Therapeutics Branch

Treatment Section

Smartphone Delivery Of Mobile HIV Risk Reduction Education. Phillips KA, Epstein DH, Mezghanni M, Vahabzadeh M, Reamer D, Agage D, Preston KL. AIDS Res Treat. 2013; 2013:231956. doi: 10.1155/2013/231956. Epub 2013 Sep 17.
The authors sought to develop and deploy a video-based smartphone-delivered mobile HIV Risk Reduction (mHIVRR) intervention to individuals in an addiction treatment clinic. They developed 3 video modules that consisted of a 10-minute HIVRR video, 11 acceptability questions, and 3 knowledge questions and deployed them as a secondary study within a larger study of ecological momentary and geographical momentary assessments. All 24 individuals who remained in the main study long enough completed the mHIVRR secondary study. All 3 videos met the authors'a priori criteria for acceptability "as is" in the population: they achieved median scores of ≤2.5 on a 5-point Likert scale; ≤20% of the individuals gave them the most negative rating on the scale; a majority of the individuals stated that they would not prefer other formats over video-based smartphone-delivered one (all $P < 0.05$). Additionally, all of their video modules met the authors' a priori criteria for feasibility: ≤20% of data were missing due to participant noncompliance and ≤20% were missing due to technical failure. The authors concluded that video-based mHIVRR education delivered via smartphone is acceptable, feasible and may increase HIV/STD risk reduction knowledge. Future studies, with pre-intervention assessments of knowledge and random assignment, are needed to confirm these findings.

Daily Temporal Patterns of Heroin and Cocaine Use and Craving: Relationship With Business Hours Regardless Of Actual Employment Status. Phillips KA, Epstein DH, Preston KL. Addict Behav. 2013 Oct; 38(10): 248524-91. doi: 10.1016/j.addbeh.2013.05.010. Epub 2013 May 22.
Real-time monitoring of behavior using Ecological Momentary Assessment (EMA) has provided detailed data about daily temporal patterns of craving and use in cigarette smokers. The authors have collected similar data from a sample of cocaine and heroin users. Here they analyzed it in the context of its relationship with a societal construct of daily temporal organization: 9-to-5 business hours. In a 28-week prospective study, 112 methadone-maintained polydrug-abusing

individuals initiated an electronic-diary entry and provided data each time they used cocaine, heroin, or both during weeks 4 to 28. EMA data were collected for 10,781 person-days and included: 663 cocaine-craving events, 710 cocaine-use events, 288 heroin-craving events, 66 heroin-use events, 630 craving-both-drugs events, and 282 use-of-both-drugs events. At baseline, 34% of the participants reported full-time employment in the preceding 3-year period. Most participants' current employment status fluctuated throughout the study. In a generalized linear mixed model (SAS Proc Glimmix), cocaine use varied by time of day relative to business hours ($p<0.0001$) and there was a significant interaction between Day of the Week and Time Relative to Business Hours ($p<0.002$) regardless of current work status. Cocaine craving also varied by time of day relative to business hours ($p<0.0001$), however, there was no significant interaction between Day of the Week and Time Relative to Business Hours ($p=.57$). Heroin craving and use were mostly reported during business hours, but data were sparse. Cocaine craving is most frequent during business hours while cocaine use is more frequent after business hours. Cocaine use during business hours, but not craving, seems suppressed on most weekdays, but not weekends, suggesting that societal conventions reflected in business hours influence drug-use patterns even in individuals whose daily schedules are not necessarily dictated by employment during conventional business hours.

Therapeutics Research Branch

Identifying Methamphetamine Exposure In Children. Castaneto MS, Barnes AJ, Scheidweiler KB, Schaffer M, Rogers KK, Stewart D, Huestis MA Therapeutic Drug Monitoring 2013 Dec; 35(6): 823-830.

Methamphetamine (MAMP) use, distribution, and manufacture remain a serious public health and safety problem in the United States, and children environmentally exposed to MAMP face a myriad of developmental, social, and health risks, including severe abuse and neglect necessitating child protection involvement. It is recommended that drug-endangered children receive medical evaluation and care with documentation of overall physical and mental conditions and have urine drug testing. The primary aim of this study was to determine the best biological matrix to detect MAMP, amphetamine (AMP), methylenedioxymethamphetamine (MDMA), methylenedioxyamphetamine (MDA), and 3,4-methylenedioxyethylamphetamine (MDEA) in environmentally exposed children. Ninety-one children, environmentally exposed to household MAMP intake, were medically evaluated at the Child and Adolescent Abuse Resource and Evaluation Diagnostic and Treatment Center at the University of California, Davis Children's Hospital. MAMP, AMP, MDMA, MDA, and MDEA were quantified in urine and oral fluid (OF) by gas chromatography mass spectrometry and in hair by liquid chromatography tandem mass spectrometry. Overall drug detection rates in OF, urine, and hair were 6.9%, 22.1%, and 77.8%, respectively. Seventy children (79%) tested positive for 1 or more drugs in 1 or more matrices. MAMP was the primary analyte detected in all 3 biological matrices. All positive OF ($n = 5$), and 18 of 19 positive urine specimens also had a positive hair test.

Hair analysis offered a more sensitive tool for identifying MAMP, AMP, and MDMA environmental exposure in children than urine or OF testing. A negative urine or hair test does not exclude the possibility of drug exposure, but hair testing provided the greatest sensitivity for identifying drug-exposed children.

3,4-Methylenedioxymethamphetamine (MDMA) and Metabolites Disposition In Blood and Plasma Following Controlled Oral Administration. Hartman RL, Desrosiers NA, Barnes AJ, Yun K, Scheidweiler KB, Kolbrich-Spargo EA, Gorelick DA, Goodwin RS, Huestis MA. Analytical and Bioanalytical Chemistry 2013; e-pub November 15, 2013.
3,4-Methylenedioxymethamphetamine (MDMA) is an illicit phenethylamine ingested for entactogenic and euphoric effects. Although blood is more commonly submitted for forensic analysis, previous human MDMA pharmacokinetics research focused on plasma data; no direct blood-plasma comparisons were drawn. Blood and plasma specimens from 50 healthy adult volunteers (33 males, 17 females, 36 African-American) who ingested recreational 1.0 and 1.6 mg/kg MDMA doses were quantified for MDMA and metabolites 4-hydroxy-3-methoxymethamphetamine (HMMA), 3,4-methylenedioxyamphetamine (MDA), and 4-hydroxy-3-methoxyamphetamine (HMA) by two-dimensional gas chromatography-mass spectrometry. Specimens were collected up to 3 h post-dose and evaluated for maximum concentration (Cmax), first detection time (tfirst), time of Cmax (tmax), and 3-h area under the curve (AUC0-3 h); as well as blood metabolite ratios and blood/plasma ratios. Median blood MDMA and MDA Cmax were significantly greater ($p<0.0005$) than in plasma, but HMMA was significantly less ($p<0.0005$). HMA was detected in few blood specimens, at low concentrations. Nonlinear pharmacokinetics were not observed for MDMA or MDA in this absorptive phase, but HMMA Cmax and AUC0-3 h were similar for both doses despite the 1.6-fold dose difference. Blood MDA/MDMA and MDA/HMMA significantly increased ($p<0.0001$) over the 3-h time course, and HMMA/MDMA significantly decreased ($p<0.0001$). Blood MDMA Cmax was significantly greater in females ($p=0.010$) after the low dose only. Low-dose HMMA AUC0-3 h was significantly decreased in females' blood and plasma ($p=0.027$) and in African-Americans' plasma ($p=0.035$). These data provide valuable insight into MDMA blood-plasma relationships for forensic interpretation and evidence of sex- and race-based differential metabolism and risk profiles.

Urinary Cannabinoids Disposition In Occasional and Frequent Smokers: Is THC-Glucuronide In Sequential Urine Samples a Marker Of Recent Use In Frequent Smokers? Desrosiers NA, Lee D, Concheiro M, Scheidweiler KB, Gorelick DA, Huestis MA. Clinical Chemistry 2013; e-pub November 1, 2013.
There is extended urinary excretion of Δ9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) in abstinent frequent cannabis smokers. The authors characterized THC, 11-OH-THC, THCCOOH, cannabidiol, cannabinol, THC-glucuronide, and THCCOOH-glucuronide disposition in urine of frequent and occasional cannabis smokers, and propose a model to predict recent cannabis smoking. Frequent and occasional smokers resided on a closed research unit and smoked one 6.8% THC cannabis cigarette ad libitum. Urinary cannabinoids were quantified in each void by liquid chromatography tandem mass spectrometry within 24 h of collection. No urine samples had measureable THC, 11- OH-THC, cannabidiol, or cannabinol. THCCOOH, THC-glucuronide, and THCCOOH-glucuronide were measurable in all frequent smokers' urine and 60%, 100%, and 100% of occasional smokers' urine samples, respectively. Pre- and postdose maximal concentrations (non- and creatinine normalized) and probability of being positive were significantly higher in frequent smokers' samples. THC-glucuronide concentrations peaked 0.6–7.4 h after smoking; THCCOOH and THCCOOH-glucuronide concentrations were highly variable. At the newly adopted THCCOOH 175-µg/L World Anti-Doping Agency decision limit,

only 50% of frequent smokers were positive 0–6 h postdose; no occasional smokers' samples were positive. An absolute %difference of ≥50% between 2 consecutive THC-glucuronide–positive samples with a creatinine normalized concentration of ≥2 μg/g in the first sample predicted cannabis smoking with efficiencies of 93.1% in frequent and 76.9% in occasional smokers within 6 h of first sample collection. These controlled urinary cannabinoid data provide a possible means of identifying recent cannabis intake in cannabis smokers' urine within a short collection time frame after smoking.

Simultaneous Quantification of 28 Synthetic Cathinones and Metabolites In Urine By Liquid Chromatography-High Resolution Mass Spectrometry. Concheiro M, Anizan S, Ellefsen K, Huestis MA Analytical and Bioanalytical Chemistry 2013 Nov; 405(29): 9437-9448.
Synthetic cathinones are novel stimulants derived from cathinone, with amphetamines or cocaine-like effects, often labeled "not for human consumption" and considered "legal highs". Emergence of these new designer drugs complicate interpretation of forensic and clinical cases, with introduction of many new analogs designed to circumvent legislation and vary effects and potencies. The authors developed a method for the simultaneous quantification of 28 synthetic cathinones, including four metabolites, in urine by liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS). These cathinones include cathinone, methcathinone, and synthetic cathinones position-3'-substituted, N-alkyl-substituted, ring-substituted, methylenedioxy-substituted, and pyrrolidinyl-substituted. One mL phosphate buffer pH 6 and 25 μL IStd solution were combined with 0.25 mL urine, and subjected to solid phase cation exchange extraction (SOLA SCX). The chromatographic reverse-phase separation was achieved with a gradient mobile phase of 0.1 % formic acid in water and in acetonitrile in 20 min. The authors employed a Q Exactive high resolution mass spectrometer, with compounds identified and quantified by target-MSMS experiments. The assay was linear from 0.5-1 to 100 μg/L, with limits of detection of 0.25-1 μg/L. Imprecision (n=20) was <15.9 % and accuracy (n=20) 85.2-118.1 %. Extraction efficiency was 78.9-116.7 % (CV 1.4-16.7 %, n=5), process efficiency 57.7-104.9 %, and matrix effects from -29.5 % to 1.5 % (CV 1.9-13.1 %, n=10). Most synthetic cathinones were stable at 4 °C for 72 h (n=27) and after 3 freeze-thaw cycles (n=26), but many (n=19) were not stable at room temperature for 24 h (losses up to -67.6 %). The method was applied to authentic urine specimens from synthetic cathinone users. This method provides a comprehensive confirmation method for 28 synthetic cathinones in urine, with good selectivity and specificity.

First Metabolic Profile Of XLR-11, A Novel Synthetic Cannabinoid, Obtained By Using Human Hepatocytes and High-Resolution Mass Spectrometry. Wohlfarth A, Pang S, Zhu M, Gandhi AS, Scheidweiler KB, Liu HF, Huestis MA. Clinical Chemistry 2013 Nov: 59(11): 1638-1648.
Since the mid-2000s synthetic cannabinoids have been abused as recreational drugs, prompting scheduling of these substances in many countries. To circumvent legislation, manufacturers constantly market new compounds; [1-(5-fluoropentyl)indol-3-yl]-(2,2,3,3-tetramethyl-cyclopropyl)methanone (XLR-11), the fluorinated UR-144 analog, is one of the most recent and widely abused drugs, and its use is now linked with acute kidney injury. The authors'goal was to investigate XLR-11 metabolism for identification of major urinary targets in analytical methods and to clarify the origin of metabolites when one or more parent synthetic cannabinoids can be the source. They incubated 10 μmol/L XLR-11 with pooled human hepatocytes and sampled

after 1 and 3 h. Samples were analyzed by high-resolution mass spectrometry with a TOF scan followed by information-dependent acquisition triggered product ion scans with dynamic background subtraction and mass defect filters. Scans were thoroughly data mined with different data processing algorithms (Metabolite Pilot 1.5). XLR-11 underwent phase I and II metabolism, producing more than 25 metabolites resulting from hydroxylation, carboxylation, hemiketal and hemiacetal formation, internal dehydration, and further glucuronidation of some oxidative metabolites. No sulfate or glutathione conjugation was observed. XLR-11 also was defluorinated, forming UR-144 metabolites. On the basis of mass spectrometry peak areas, the authors determined that the major metabolites were 2′-carboxy-XLR-11, UR-144 pentanoic acid, 5-hydroxy-UR-144, hydroxy-XLR-11 glucuronides, and 2′-carboxy-UR-144 pentanoic acid. Minor metabolites were combinations of the biotransformations mentioned above, often glucuronidated. These are the first data defining major urinary targets of XLR-11 metabolism that could document XLR-11 intake in forensic and clinical investigations.

The Potential Role Of Oral Fluid In Antidoping Testing. Anizan S and Huestis MA. Clinical Chemistry 2013; e-pub October 23, 2013.
Currently, urine and blood are the only matrices authorized for antidoping testing by the World Anti-Doping Agency (WADA). Although the usefulness of urine and blood is proven, issues remain for monitoring some drug classes and for drugs prohibited only in competition. The alternative matrix oral fluid (OF) may offer solutions to some of these issues. OF collection is easy, noninvasive, and sex neutral and is directly observed, limiting potential adulteration, a major problem for urine testing. OF is used to monitor drug intake in workplace, clinical toxicology, criminal justice, and driving under the influence of drugs programs and potentially could complement urine and blood for antidoping testing in sports. This review outlines the present state of knowledge and the advantages and limitations of OF testing for each of the WADA drug classes and the research needed to advance OF testing as a viable alternative for antidoping testing. Doping agents are either prohibited at all times or prohibited in competition only. Few OF data from controlled drug administration studies are available for substances banned at all times, whereas for some agents prohibited only in competition, sufficient data may be available to suggest appropriate analytes and cutoffs (analytical threshold concentrations) to identify recent drug use. Additional research is needed to characterize the disposition of many banned substances into OF; OF collection methods and doping agent stability in OF also require investigation to allow the accurate interpretation of OF tests for antidoping monitoring.

Nonlinear Pharmacokinetics Of ({+/-})3,4-Methylenedioxymethamphetamine (MDMA) and Its Pharmacodynamic Consequences In the Rat. Concheiro M, Baumann MH, Scheidweiler KB, Rothman RB, Marrone GF, Huestis MA. Drug Metabolism and Disposition 2013; e-pub October 18, 2013.
3,4-Methylenedioxymethamphetamine (MDMA) is a widely abused illicit drug that can cause severe and even fatal adverse effects. However, interest remains for its possible clinical applications in post-traumatic stress disorder and anxiety treatment. Preclinical studies to determine MDMA's safety are needed. The authors evaluated MDMA pharmacokinetics and metabolism in male rats receiving 2.5, 5 and 10 mg/kg subcutaneous MDMA, and the associated pharmacodynamic consequences. Blood was collected via jugular catheter at 0, 0.5, 1, 2, 4, 6, 8, 16 and 24 h, with simultaneous serotonin (5-HT) behavioral syndrome and core temperature monitoring. Plasma specimens were analyzed for MDMA and metabolites (±)-3,4

dihydroxymethamphetamine (HHMA), (±)-4-hydroxy-3-methoxymethamphetamine (HMMA) and (±)-3,4-methylenedioxyamphetamine (MDA) by liquid chromatography-tandem mass spectrometry. After 2.5 mg/kg MDMA, mean maximum MDMA concentration was 164±47.1 ng/ml, HHMA and HMMA were major metabolites, and <20% MDMA was metabolized to MDA. After 5 and 10 mg/kg doses, MDMA areas-under-the-curve (AUC) were 3- and 10-fold greater than those after 2.5 mg/kg; HHMA and HMMA AUC values were relatively constant across doses, while MDA AUC values were greater than dose proportional. These data provide decisive in vivo evidence that MDMA and MDA display nonlinear accumulation via metabolic auto-inhibition in the rat. Importantly, 5-HT syndrome severity correlated with MDMA concentrations ($r=0.8083$, $p<0.0001$), while core temperature correlated with MDA concentrations ($r=0.7595$, $p<0.0001$), suggesting MDMA's behavioral and hyperthermic effects may involve distinct mechanisms. Given key similarities between MDMA pharmacokinetics in rats and humans, data from rats can be useful when provided at clinically-relevant doses.

First Characterization Of AKB-48 Metabolism, a Novel Synthetic Cannabinoid, Using Human Hepatocytes and High-Resolution Mass Spectrometry. Gandhi AS, Zhu M, Pang S, Wohlfarth A, Scheidweiler KB, Liu HF, Huestis MA. The American Association of Pharmaceutical Journal 2013 Oct; 15(4): 1091-1098.

Since the federal authorities scheduled the first synthetic cannabinoids, JWH-018 and JWH-073, new synthetic cannabinoids were robustly marketed. N-(1-Adamantyl)-1-pentylindazole-3-carboxamide (AKB-48), also known as APINACA, was recently observed in Japanese herbal smoking blends. The National Forensic Laboratory Information System registered 443 reports of AKB-48 cases in the USA from March 2010 to January 2013. In May 2013, the Drug Enforcement Administration listed AKB-48 as a Schedule I drug. Recently, AKB-48 was shown to have twice the CB1 receptor binding affinity than CB2. These pharmacological effects and the difficulty in detecting the parent compound in urine highlight the importance of metabolite identification for developing analytical methods for clinical and forensic investigations. Using human hepatocytes and TripleTOF mass spectrometry, the authors identified 17 novel phase I and II AKB-48 metabolites, products of monohydroxylation, dihydroxylation, or trihydroxylation on the aliphatic adamantane ring or N-pentyl side chain. Glucuronide conjugation of some mono- and dihydroxylated metabolites also occurred. Oxidation and dihydroxylation on the adamantane ring and N-pentyl side chain formed a ketone. More metabolites were identified after 3 h of incubation than at 1 h. For the first time, the authors present a AKB-48 metabolic scheme obtained from human hepatocytes and high-resolution mass spectrometry. These data are needed to develop analytical methods to identify AKB-48 consumption in clinical and forensic testing.

Oral Fluid Cannabinoid Concentrations Following Controlled Smoked Cannabis In Chronic Frequent and Occasional Smokers. Anizan S, Milman G, Desrosiers N, Barnes AJ, Gorelick DA, Huestis MA. Analytical and Bioanalytical Chemistry 2013 Oct; 405(26): 8451-8461.

Oral fluid (OF) is an alternative biological matrix for monitoring cannabis intake in drug testing, and drugged driving (DUID) programs, but OF cannabinoid test interpretation is challenging. Controlled cannabinoid administration studies provide a scientific database for interpreting cannabinoid OF tests. The authors compared differences in OF cannabinoid concentrations from 19 h before to 30 h after smoking a 6.8 % THC cigarette in chronic frequent and occasional

cannabis smokers. OF was collected with the Statsure Saliva Sampler™ OF device. 2D-GC-MS was used to quantify cannabinoids in 357 OF specimens; 65 had inadequate OF volume within 3 h after smoking. All OF specimens were THC-positive for up to 13.5 h after smoking, without significant differences between frequent and occasional smokers over 30 h. Cannabidiol (CBD) and cannabinol (CBN) had short median last detection times (2.5-4 h for CBD and 6-8 h for CBN) in both groups. THCCOOH was detected in 25 and 212 occasional and frequent smokers' OF samples, respectively. THCCOOH provided longer detection windows than THC in all frequent smokers. As THCCOOH is not present in cannabis smoke, its presence in OF minimizes the potential for false positive results from passive environmental smoke exposure, and can identify oral THC ingestion, while OF THC cannot. THC≥1 μg/L, in addition to CBD≥1 μg/L or CBN≥1 μg/L suggested recent cannabis intake (≤13.5 h), important for DUID cases, whereas THC≥1 μg/L or THC≥2 μg/L cutoffs had longer detection windows (≥30 h), important for workplace testing. THCCOOH windows of detection for chronic, frequent cannabis smokers extended beyond 30 h, while they were shorter (0-24 h) for occasional cannabis smokers.

Around-The-Clock Oral THC Effects On Sleep In Male Chronic Daily Cannabis Smokers. Gorelick DA, Goodwin RS, Schwilke E, Schroeder JR, Schwope DM, Kelly DL, Ortemann-Renon C, Bonnet D, Huestis MA. The American Journal on Addictions 2013 Sep-Oct ;22(5): 510-514.

Δ9-tetrahydrocannabinol (THC) promotes sleep in animals; clinical use of THC is associated with somnolence. Human laboratory studies of oral THC have not shown consistent effects on sleep. The authors prospectively evaluated self-reported sleep parameters during controlled oral THC administration to research volunteers. Thirteen male chronic daily cannabis smokers (mean±SD age 24.6±3.7 years, self-reported smoking frequency of 5.5±5.9 (range 1-24) joint-equivalents daily at study entry) were administered oral THC doses (20mg) around-the-clock for 7 days (40-120mg daily) starting the afternoon after admission. The St. Mary's Hospital Sleep Questionnaire was completed every morning. Plasma THC and 11-OH-THC (active metabolite) concentrations were measured in venous blood samples collected every evening. Changes in sleep characteristics over time and associations between sleep characteristics and plasma cannabinoid concentrations were evaluated with repeated measures mixed linear regression. Higher evening THC and 11-OH-THC concentrations were significantly associated with shorter sleep latency, less difficulty falling asleep, and more daytime sleep the following day. In contrast, the duration of calculated and self-reported nighttime sleep decreased slightly (3.54 and 5.34 minutes per night, respectively) but significantly during the study. These findings suggest that tolerance to the somnolent effects of THC may have occurred, but results should be considered preliminary due to design limitations. Somnolence from oral THC may dissipate with chronic, high-dose use. This has implications for patients who may take chronic oral THC for medicinal purposes, including cannabis dependence treatment.

Plasma Cannabinoid Concentrations During Dronabinol Pharmacotherapy For Cannabis Dependence. Milman G, Bergamaschi M, Lee D, Mendu DR, Barnes AJ, Vandrey R, Huestis MA. Therapeutic Drug Monitoring 2013 Sep 24. [Epub ahead of print].

Recently, high-dose oral synthetic delta-9-tetrahydrocannabinol (THC) was shown to alleviate cannabis withdrawal symptoms. The present data describe cannabinoid pharmacokinetics in chronic, daily cannabis smokers who received high-dose oral THC pharmacotherapy and later a smoked cannabis challenge. Eleven daily cannabis smokers received 0, 30, 60, or 120 mg/d

THC for four 5-day medication sessions, each separated by 9 days of ad libitum cannabis smoking. On the fifth day, participants were challenged with smoking one 5.9% THC cigarette. Plasma collected on the first and fifth days was quantified by two-dimensional gas chromatography mass spectrometer for THC, 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH). Linear ranges (ng/mL) were 0.5-100 for THC, 1-50 for 11-OH-THC, and 0.5-200 for THCCOOH. During placebo dosing, THC, 11-OH-THC, and THCCOOH concentrations consistently decreased, whereas all cannabinoids increased dose dependently during active dronabinol administration. THC increase over time was not significant after any dose, 11-OH-THC increased significantly during the 60- and 120-mg/d doses, and THCCOOH increased significantly only during the 120-mg/d dose. THC, 11-OH-THC, and THCCOOH concentrations peaked within 0.25 hours after cannabis smoking, except after 120 mg/d THC when THCCOOH peaked 0.5 hours before smoking. The significant withdrawal effects noted during placebo dronabinol administration were supported by significant plasma THC and 11-OH-THC concentration decreases. During active dronabinol dosing, significant dose-dependent increases in THC and 11-OH-THC concentrations support withdrawal symptom suppression. THC concentrations after cannabis smoking were only distinguishable from oral THC doses for 1 hour, too short a period to feasibly identify cannabis relapse. THCCOOH/THC ratios were higher 14 hours after overnight oral dronabinol abstinence but cannot distinguish oral THC dosing from the smoked cannabis intake.

Cannabinoids In Exhaled Breath Following Controlled Administration Of Smoked Cannabis. Himes SK, Scheidweiler KB, Beck O, Gorelick DA, Desrosiers NA, Huestis MA, Analytical and Bioanalytical Chemistry 2013; e-pub September 17, 2013.
Δ9-Tetrahydrocannabinol (THC), 11-nor-9-carboxy-THC (THCCOOH), and cannabinol (CBN) were measured in breath following controlled cannabis smoking to characterize the time course and window of detection of breath cannabinoids. Exhaled breath was collected from chronic (≥4 times per week) and occasional (<twice per week) smokers before and after smoking a 6.8% THC cigarette. Sample analysis included methanol extraction from breath pads, solid-phase extraction, and liquid chromatography-tandem mass spectrometry quantification.
THC was the major cannabinoid in breath; no sample contained THCCOOH and only 1 contained CBN. Among chronic smokers (n = 13), all breath samples were positive for THC at 0.89 h, 76.9% at 1.38 h, and 53.8% at 2.38 h, and only 1 sample was positive at 4.2 h after smoking. Among occasional smokers (n = 11), 90.9% of breath samples were THC-positive at 0.95 h and 63.6% at 1.49 h. One occasional smoker had no detectable THC. Analyte recovery from breath pads by methanolic extraction was 84.2%-97.4%. Limits of quantification were 50 pg/pad for THC and CBN and 100 pg/pad for THCCOOH. Solid-phase extraction efficiency was 46.6%-52.1% (THC) and 76.3%-83.8% (THCCOOH, CBN). Matrix effects were -34.6% to 12.3%. Cannabinoids fortified onto breath pads were stable (≤18.2% concentration change) for 8 h at room temperature and -20°C storage for 6 months. Breath may offer an alternative matrix for testing for recent driving under the influence of cannabis, but is limited to a short detection window (0.5-2 h).

Oral Fluid/Plasma Ratios Following Controlled Oral THC and Smoked Cannabis Administration. Lee D, Vandrey R, Milman G, Bergamaschi M, Mendu DR, Murray JA, Barnes AJ, Huestis, MA. Analytical and Bioanalytical Chemistry. 2013 Sep; 405(23): 7269-7279.
Oral fluid (OF) is a valuable biological alternative for clinical and forensic drug testing. Evaluating OF to plasma (OF/P) cannabinoid ratios provides important pharmacokinetic data on the disposition of drug and factors influencing partition between matrices. Eleven chronic cannabis smokers resided on a closed research unit for 51 days. There were four 5-day sessions of 0, 30, 60, and 120 mg oral Δ(9)-tetrahydrocannabinol (THC)/day followed by a five-puff smoked cannabis challenge on Day 5. Each session was separated by 9 days ad libitum cannabis smoking. OF and plasma specimens were analyzed for THC and metabolites. During ad libitum smoking, OF/P THC ratios were high (median, 6.1; range, 0.2-348.5) within 1 h after last smoking, decreasing to 0.1-20.7 (median, 2.1) by 13.0-17.1 h. OF/P THC ratios also decreased during 5-days oral THC dosing, and after the smoked cannabis challenge, median OF/P THC ratios decreased from 1.4 to 5.5 (0.04-245.6) at 0.25 h to 0.12 to 0.17 (0.04-5.1) at 10.5 h post-smoking. In other studies, longer exposure to more potent cannabis smoke and oromucosal cannabis spray was associated with increased OF/P THC peak ratios. Median OF/P 11-nor-9-carboxy-THC (THCCOOH) ratios were 0.3-2.5 (range, 0.1-14.7) ng/μg, much more consistent in various dosing conditions over time. OF/P THC, but not THCCOOH, ratios were significantly influenced by oral cavity contamination after smoking or oromucosal spray of cannabinoid products, followed by time-dependent decreases. Establishing relationships between OF and plasma cannabinoid concentrations is essential for making inferences of impairment or other clinical outcomes from OF concentrations.

Cross-National Comparison Of Prenatal Methamphetamine Exposure On Infant and Early Child Physical Growth: A Natural Experiment. Abar B, LaGasse LL, Wouldes T, Derauf C, Newman E, Shah R, Smith LM, Arria AM, Huestis MA, DellaGrotta, Dansereau LM, Wilcox T, Neal CR, Lester BM. Prevention Science 2013 Aug 13. [Epub ahead of print].
The current study seeks to compare the effects of prenatal methamphetamine exposure (PME) on infant and child physical growth between the USA and New Zealand (NZ). This cross-national comparison provides a unique opportunity to examine the potential impact of services provided to drug using mothers on child health. The longitudinal Infant Development, Environment and Lifestyle study of PME from birth to 36 months was conducted in the USA and NZ. The US cohort included 204 children with PME and 212 non-PME matched comparisons (NPME); the NZ cohort included 108 children with PME and 115 NPME matched comparisons. Latent growth curve models were used to examine effects of PME, country of origin, and the country×PME interaction on growth in length/height and weight. In regard to length/height, PME and country of origin were associated with initial length and growth over time. There was also a significant interaction effect, such that children with PME in the USA were shorter at birth than children with PME in NZ after controlling for other prenatal exposures, infant set, socioeconomic status, and maternal height. In regard to weight, there was only an effect of country of origin. Effects of PME on infant and child growth were shown to differ across countries, with exposed children in NZ faring better than exposed children in the USA. Implications for prevention programs and public policy are discussed.

Oral Fluid Cannabinoids In Chronic Cannabis Smokers During Oral Δ9-Tetrahydrocannabinol Therapy and Smoked Cannabis Challenge. Lee DL, Vandrey R, Mendu DR, Anizan S, Milman G, Murray JA, Barnes AJ, Huestis MA. Clinical Chemistry 2013; e-pub August 12, 2013.

Oral Δ9-tetrahydrocannabinol (THC) is effective for attenuating cannabis withdrawal and may benefit treatment of cannabis use disorders. Oral fluid (OF) cannabinoid testing, increasing in forensic and workplace settings, could be valuable for monitoring during cannabis treatment. Eleven cannabis smokers resided on a closed research unit for 51 days and received daily 0, 30, 60, and 120 mg of oral THC in divided doses for 5 days. There was a 5-puff smoked cannabis challenge on the fifth day. Each medication session was separated by 9 days of ad libitum cannabis smoking. OF was collected the evening before and throughout oral THC sessions and analyzed by 2-dimensional GC-MS for THC, cannabidiol (CBD), cannabinol (CBN), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH). During all oral THC administrations, THC OF concentrations decreased to ≤78.2, 33.2, and 1.4 μ g/L by 24, 48, and 72 h, respectively. CBN also decreased over time, with concentrations 10-fold lower than THC, with none detected beyond 69 h. CBD and 11-OH-THC were rarely detected, only within 19 and 1.6 h after smoking, respectively. THCCOOH OF concentrations were dose dependent and increased over time during 120-mg THC dosing. After cannabis smoking, THC, CBN, and THCCOOH concentrations showed a significant dose effect and decreased significantly over time. Oral THC dosing significantly affected OF THCCOOH but minimally contributed to THC OF concentrations; prior ad libitum smoking was the primary source of THC, CBD, and CBN. Higher cannabinoid concentrations following active oral THC administrations vs placebo suggest a compensatory effect of THC tolerance on smoking topography.

Current Knowledge On Cannabinoids In Oral Fluid. Lee D, Huestis, MA. Drug Testing and Analysis, e-pub August 25, 2013.

Oral fluid (OF) is a new biological matrix for clinical and forensic drug testing, offering non-invasive and directly observable sample collection reducing adulteration potential, ease of multiple sample collections, lower biohazard risk during collection, recent exposure identification, and stronger correlation with blood than urine concentrations. Because cannabinoids are usually the most prevalent analytes in illicit drug testing, application of OF drug testing requires sufficient scientific data to support sensitive and specific OF cannabinoid detection. This review presents current knowledge of OF cannabinoids, evaluating pharmacokinetic properties, detection windows, and correlation with other biological matrices and impairment from field applications and controlled drug administration studies. In addition, onsite screening technologies, confirmatory analytical methods, drug stability, and effects of sample collection procedure, adulterants, and passive environmental exposure are reviewed. Delta-9-tetrahydrocannabinol OF concentrations could be >1000μg/L shortly after smoking, whereas minor cannabinoids are detected at 10-fold and metabolites at 1000-fold lower concentrations. OF research over the past decade demonstrated that appropriate interpretation of test results requires a comprehensive understanding of distinct elimination profiles and detection windows for different cannabinoids, which are influenced by administration route, dose, and drug use history. Thus, each drug testing program should establish cut-off criteria, collection/analysis procedures, and storage conditions tailored to its purposes. Building a scientific basis for OF testing is ongoing, with continuing OF cannabinoids research on passive environmental exposure, drug use history, donor physiological conditions, and oral cavity

metabolism needed to better understand mechanisms of cannabinoid OF disposition and expand OF drug testing applicability.

Integrative Neuroscience Branch

Cellular Pathobiology Section

Sigma-1 Receptor Chaperone at the ER-Mitochondrion Interface Mediates Mitochondrion-ER-Nucleus Signaling For Cellular Survival. Mori P, Hayashi T, Hayashi E, Su TP. PLoS One. 2013 Oct 18; 8(10):e76941. doi: 10.1371/journal.pone.0076941.
The membrane of the endoplasmic reticulum (ER) of a cell forms contacts directly with mitochondria whereby the contact is referred to as the mitochondrion-associated ER membrane or the MAM. Here the authors found that the MAM regulates cellular survival via an MAM-residing ER chaperone the sigma-1 receptor (Sig-1R) in that the Sig-1R chaperones the ER stress sensor IRE1 to facilitate inter-organelle signaling for survival. IRE1 is found in this study to be enriched at the MAM in CHO cells. They found that IRE1 is stabilized at the MAM by Sig-1Rs when cells are under ER stress. Sig-1Rs stabilize IRE1 and thus allow for conformationally correct IRE1 to dimerize into the long-lasting, activated endonuclease. The IRE1 at the MAM also responds to reactive oxygen species derived from mitochondria. Therefore, the ER-mitochondrion interface serves as an important subcellular entity in the regulation of cellular survival by enhancing the stress-responding signaling between mitochondria, ER, and nucleus.

Molecular Neuropsychiatry Research Branch

Methamphetamine Downregulates Striatal Glutamate Receptors Via Diverse Epigenetic Mechanisms. Jayanthi S, McCoy MT, Chen B, Britt JP, Kourrich S, Yau HJ, Ladenheim B, Krasnova IN, Bonci A, Cadet JL. Biol Psychiatry. 2013 Oct 16. pii: S0006-3223(13)00915-3. doi: 10.1016/j.biopsych.2013.09.034. [Epub ahead of print].
Chronic METH decreased transcript and protein expression of GluA1 and GluA2 alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and GluN1 N-methyl-D-aspartate receptor subunits. These changes were associated with altered electrophysiological glutamatergic responses in striatal neurons. Chromatin immunoprecipitation-polymerase chain reaction revealed that METH decreased enrichment of acetylated histone H4 on GluA1, GluA2, and GluN1 promoters. Methamphetamine exposure also increased repressor element-1 silencing transcription factor (REST) corepressor 1, methylated CpG binding protein 2, and histone deacetylase 2 enrichment, but not of sirtuin 1 or sirtuin 2, onto GluA1 and GluA2 gene sequences. Moreover, METH caused interactions of REST corepressor 1 and methylated CpG binding protein 2 with histone deacetylase 2 and of REST with histone deacetylase 1. Surprisingly, methylated DNA immunoprecipitation and hydroxymethylated DNA immunoprecipitation-polymerase chain reaction revealed METH-induced decreased enrichment of 5-methylcytosine and 5-hydroxymethylcytosine at GluA1 and GluA2 promoter sequences. Importantly, the histone deacetylase inhibitor, valproic acid, blocked METH-induced decreased expression of AMPAR and N-methyl-D-aspartate receptor subunits. Finally, valproic acid also attenuated METH-induced decrease H4K16Ac recruitment on AMPAR gene sequences. These

observations suggest that histone H4 hypoacetylation may be the main determinant of METH-induced decreased striatal glutamate receptor expression.

Neuronal Expression Of Familial Parkinson's Disease A53T A-Synuclein Causes Early Motor Impairment, Reduced Anxiety and Potential Sleep Disturbances In Mice. Rothman SM, Griffioen KJ, Vranis N, Ladenheim B, Cong WN, Cadet JL, Haran J, Martin B, Mattson MP. J Parkinsons Dis. 2013; 3(2): 215-229. doi: 10.3233/JPD-120130.
Mutations in the human α-synuclein gene lead to early-onset Parkinson's disease (PD); however, phenotypes of α-synuclein mutant mice vary depending upon the promoter driving transgene expression. The goal of this study was to characterize behavior and neurochemical alterations in mice expressing mutant (A53T) human α-synuclein, controlled by a neuron-specific Thy-1 promoter. These data provide important additional phenotypic and biochemical characterization of a previously generated model of PD. A53T (SNCA) and wild type (WT) littermate mice were evaluated for motor function (rotarod and stride length) and anxiety (elevated plus maze and open field) every 2 weeks. At 24 weeks mice were evaluated in a Comprehensive Lab Animal Monitoring System (CLAMS). A separate cohort of mice were euthanized at 12, 24 and 36 weeks for immunoblot analysis of α-synuclein, dopamine transporter (DAT) and tyrosine hydroxylase (TH) in the striatum, and hypothalamic serotonin and metabolites were measured. SNCA mice display significant motor deficits at 14-18 weeks of age compared to WT mice, which progress over time. CLAMS analysis revealed an increase in activity during the dark phase and a reduction in overall estimated sleep time for SNCA mice compared to WT consistent with clinical reports of sleep abnormalities in PD. A transient change in the levels of DAT appeared at 12 weeks in the striatum and serotonin levels were also altered in the hypothalamus at this time point. This PD model displays consistent and clinically relevant motor and sleep phenotypes. Anxiety phenotypes are consistent with other α-synuclein based PD models yet incongruous with typical clinical symptoms. Early increases in serotonin levels potentially explain reductions in anxiety behaviors and sleep.

Genome-Wide Profiling Identifies A Subset Of Methamphetamine (METH)-Induced Genes Associated With METH-Induced Increased H4K5Ac Binding In the Rat Striatum. Cadet JL, Jayanthi S, McCoy MT, Ladenheim B, Saint-Preux F, Lehrmann E, De S, Becker KG, Brannock C. Genomics. 2013 Aug 12; 14: 545. doi: 10.1186/1471-2164-14-545.
METH is an illicit drug of abuse that influences gene expression in the rat striatum. Histone modifications regulate gene transcription. The authors therefore used microarray analysis and genome-scale approaches to examine potential relationships between the effects of METH on gene expression and on DNA binding of histone H4 acetylated at lysine 4 (H4K5Ac) in the rat dorsal striatum of METH-naïve and METH-pretreated rats. Acute and chronic METH administration caused differential changes in striatal gene expression. METH also increased H4K5Ac binding around the transcriptional start sites (TSSs) of genes in the rat striatum. In order to relate gene expression to histone acetylation, the authors binned genes of similar expression into groups of 100 genes and proceeded to relate gene expression to H4K5Ac binding. They found a positive correlation between gene expression and H4K5Ac binding in the striatum of control rats. Similar correlations were observed in METH-treated rats. Genes that showed acute METH-induced increased expression in saline-pretreated rats also showed METH-induced increased H4K5Ac binding. The acute METH injection caused similar increases in

H4K5Ac binding in METH-pretreated rats, without affecting gene expression to the same degree. Finally, genes that showed METH-induced decreased expression exhibited either decreases or no changes in H4K5Ac binding. Acute METH injections caused increased gene expression of genes that showed increased H4K5Ac binding near their transcription start sites.

Chemical Biology Research Branch

Drug Design and Synthesis Section, Chemical Biology Research Branch,

Pharmacological Characterization of the 20% Alcohol Intermittent Access Model In Sardinian Alcohol-Preferring Rats: A Model Of Binge-Like Drinking. Sabino V, Kwak J, Rice KC, Cottone P. Alcohol Clin Exp Res. 2013; 37(4): 635-643.
Binge drinking is defined as a pattern of alcohol drinking that brings blood alcohol levels to 80 mg/dl or above. In this study, the authors pharmacologically characterized the intermittent access to 20% ethanol (EtOH) model (Wise, Psychopharmacologia 1973;29:203) in Sardinian alcohol-preferring (sP) rats to determine to which of the compounds known to reduce drinking in specific animal models this binge-like drinking was sensitive to. Adult male sP rats were divided into 2 groups and allowed to drink either 20% v/v alcohol or water for 24 hours on alternate days (Monday, Wednesday, and Friday) or 10% v/v alcohol and water for 24 hours every day. After stabilization of their intake, both groups were administered 3 pharmacological agents with different mechanisms of action, naltrexone-an opioid receptor antagonist, SCH 39166-a dopamine D1 receptor antagonist, and R121919-a Corticotropin-Releasing Factor 1 (CRF1) receptor antagonist, and their effects on alcohol and water intake were determined. Intermittent 20% alcohol ("Wise") procedure in sP rats led to binge-like drinking. Alcohol drinking was suppressed by naltrexone and by SCH 39166, but not by R121919. Finally, naltrexone was more potent in reducing alcohol drinking in the intermittent 20% binge-drinking group than in the 10% continuous access drinking group. The Wise procedure in sP rats induces binge-like drinking, which appears opioid- and dopamine-receptor mediated; the CRF1 system, on the other hand, does not appear to be involved. In addition, these results suggest that naltrexone is particularly effective in reducing binge drinking. Such different pharmacological responses may apply to subtypes of alcoholic patients who differ in their motivation to drink, and may eventually contribute to treatment response.

Rimonabant Precipitates Anxiety In Rats Withdrawn From Palatable Food: Role of the Central Amygdala. Blasio A, Iemolo A, Sabino V, Petrosino S, Steardo L, Rice KC, Orlando P, Iannotti FA, Di Marzo V, Zorrilla EP, Cottone P. Neuropsychopharmacology 2013; 38(12): 2498-2507.
The anti-obesity medication rimonabant, an antagonist of cannabinoid type-1 (CB(1)) receptor, was withdrawn from the market because of adverse psychiatric side effects, including a negative affective state. The authors investigated whether rimonabant precipitates a negative emotional state in rats withdrawn from palatable food cycling. The effects of systemic administration of rimonabant on anxiety-like behavior, food intake, body weight, and adrenocortical activation were assessed in female rats during withdrawal from chronic palatable diet cycling. The levels of the endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), and the CB(1) receptor mRNA and the protein in the central nucleus of the amygdala (CeA) were also investigated.

Finally, the effects of microinfusion of rimonabant in the CeA on anxiety-like behavior, and food intake were assessed. Systemic administration of rimonabant precipitated anxiety-like behavior and anorexia of the regular chow diet in rats withdrawn from palatable diet cycling, independently from the degree of adrenocortical activation. These behavioral observations were accompanied by increased 2-AG, CB(1) receptor mRNA, and protein levels selectively in the CeA. Finally, rimonabant, microinfused directly into the CeA, precipitated anxiety-like behavior and anorexia. These data show that (i) the 2-AG-CB(1) receptor system within the CeA is recruited during abstinence from palatable diet cycling as a compensatory mechanism to dampen anxiety, and (ii) rimonabant precipitates a negative emotional state by blocking the beneficial heightened 2-AG-CB(1) receptor signaling in this brain area. These findings help elucidate the link between compulsive eating and anxiety, and it will be valuable to develop better pharmacological treatments for eating disorders and obesity.

Age-Dependent MDPV-Induced Taste Aversions and Thermoregulation In Adolescent and Adult Rats. Merluzzi AP, Hurwitz ZE, Briscione MA, Cobuzzi JL, Wetzell B, Rice KC, Riley AL. Dev Psychobiol. 2013, e-pub Oct 4, 2103.

Adolescent rats are more sensitive to the rewarding and less sensitive to the aversive properties of various drugs of abuse than their adult counterparts. Given a nationwide increase in use of "bath salts," the present experiment employed the conditioned taste aversion procedure to assess the aversive effects of 3,4-methylenedioxypyrovalerone (MDPV; 0, 1.0, 1.8, or 3.2mg/kg), a common constituent in "bath salts," in adult and adolescent rats. As similar drugs induce thermoregulatory changes in rats, temperature was recorded following MDPV administration to assess if thermoregulatory changes were related to taste aversion conditioning. Both age groups acquired taste aversions, although these aversions were weaker and developed at a slower rate in the adolescent subjects. Adolescents increased and adults decreased body temperature following MDPV administration with no correlation to aversions. The relative insensitivity of adolescents to the aversive effects of MDPV suggests that MDPV may confer an increased risk in this population.

Abuse-Related Effects Of μ-Opioid Analgesics In An Assay Of Intracranial Self-Stimulation In Rats: Modulation By Chronic Morphine Exposure. Altarifi AA, Rice KC, Negus SS. Behav Pharmacol. 2013; 24(5-6): 459-470.

Intracranial self-stimulation (ICSS) is an operant procedure in which responding is maintained by electrical brain stimulation. Stimulation frequency can be varied rapidly to maintain a wide range of baseline response rates, and drugs' effects can be evaluated simultaneously on both low ICSS rates maintained by low stimulation frequencies and high ICSS rates maintained by high stimulation frequencies. ICSS 'facilitation' indicates drug-induced increases in low ICSS rates and is often considered an abuse-related effect, whereas ICSS 'depression' indicates decreases in high ICSS rates and may indicate abuse-limiting effects. This study examined the roles of μ-agonist efficacy and of previous μ-agonist exposure as determinants of μ-agonist effects on ICSS in rats with electrodes implanted into the medial forebrain bundle. The high-efficacy, intermediate-efficacy, and low-efficacy μ agonists methadone, fentanyl, and nalbuphine were tested during escalating regimens of morphine exposure (vehicle, 3.2, and 18 mg/kg/day). During vehicle treatment, methadone and fentanyl primarily depressed ICSS, whereas nalbuphine produced weak facilitation that was not dose dependent. Chronic morphine produced tolerance to ICSS depression and increased expression of ICSS facilitation. These results suggest that μ-

agonist exposure increases the expression of abuse-related ICSS facilitation by μ agonists with a broad range of efficacies at μ receptors.

Probes For Narcotic Receptor Mediated Phenomena. 48. C7- and C8-Substituted 5-Phenylmorphan Opioids From Diastereoselective Alkylation. Lim HJ, Dersch CM, Rothman RB, Deschamps JR, Jacobson AE, Rice KC. Eur J Med Chem. 2013; 67: 335-343.
The exploration of the effect of substituents at C7 and C8 of the 5-phenylmorphans on their affinity for opioid receptors was enabled by the authors' recently introduced "one pot" diastereoselective synthesis that provided C7-oxo, hydroxy and alkyl substituents, C8-alkyl substituted 5-phenylmorphans, and compounds that had a new cyclohexane ring that includes the C7 and C8 carbon atoms of the 5-phenylmorphan. The affinity of the 5-phenylmorphans for opioid receptors is increased by a C8-methyl substituent, compared with its C7 analog. The affinity of the newly synthesized compounds is generally for the μ-opioid receptor, rather than the δ- or κ-receptors. Addition of a new cyclohexane ring to the C7 and C8 positions on the cyclohexane ring of the 5-phenylmorphans enhances μ-receptor affinity, bringing the Ki to the subnanomolar level. Unexpectedly, the N-methyl substituted compounds generally had higher affinity than comparable N-phenethyl-substituted relatives. The configurations of two compounds were determined by single-crystal X-ray crystallographic analyses.

Serotonin 2A Receptors Differentially Contribute To Abuse-Related Effects Of Cocaine and Cocaine-Induced Nigrostriatal and Mesolimbic Dopamine Overflow In Nonhuman Primates. Murnane KS, Winschel J, Schmidt KT, Stewart LM, Rose SJ, Cheng K, Rice KC, Howell LL. J Neurosci 2013: 14; 33(33): 13367-13374.
Two of the most commonly used procedures to study the abuse-related effects of drugs in laboratory animals are intravenous drug self-administration and reinstatement of extinguished behavior previously maintained by drug delivery. Intravenous self-administration is widely accepted to model ongoing drug-taking behavior, whereas reinstatement procedures are accepted to model relapse to drug taking following abstinence. Previous studies indicate that 5-HT2A receptor antagonists attenuate the reinstatement of cocaine-maintained behavior but not cocaine self-administration in rodents. Although the abuse-related effects of cocaine have been closely linked to brain dopamine systems, no previous study has determined whether this dissociation is related to differential regulation of dopamine neurotransmission. To elucidate the neuropharmacological and neuroanatomical mechanisms underlying this phenomenon, the authors evaluated the effects of the selective 5-HT2A receptor antagonist M100907 on intravenous cocaine self-administration and drug- and cue-primed reinstatement in rhesus macaques (Macaca mulatta). In separate subjects, the authors evaluated the role of 5-HT2A receptors in cocaine-induced dopamine overflow in the nucleus accumbens (n = 4) and the caudate nucleus (n = 5) using in vivo microdialysis. Consistent with previous studies, M100907 (0.3 mg/kg, i.m.) significantly attenuated drug- and cue-induced reinstatement but had no significant effects on cocaine self-administration across a range of maintenance doses. Importantly, M100907 (0.3 mg/kg, i.m.) attenuated cocaine-induced (1.0 mg/kg, i.v.) dopamine overflow in the caudate nucleus but not in the nucleus accumbens. These data suggest that important abuse-related effects of cocaine are mediated by distinct striatal dopamine projection pathways.

The Role of the Neurokinin-1 Receptor In Stress-Induced Reinstatement Of Alcohol and Cocaine Seeking. Schank JR, King CE, Sun H, Cheng K, Rice KC, Heilig M, Weinshenker D, Schroeder JP. Neuropsychopharmacology 2013, epub Oct 3, 2013.
Neurokinin-1 receptors (NK1R) have been shown to mediate alcohol and opiate, but not cocaine reward in rodents. The authors recently reported that NK1R antagonism also blocks stress-induced reinstatement of alcohol seeking in rats, but it is presently unknown whether these anti-relapse properties extend to other drug classes. Although some work has suggested that intracranial substance P (SP) infusion reinstates cocaine seeking following extinction, no studies have indicated a direct role for the NK1R in reinstatement of cocaine seeking. Here, the authors explored the effect of the NK1R antagonist L822429 on yohimbine-induced reinstatement of alcohol or cocaine seeking in Long-Evans rats. Consistent with their previous findings with footshock-induced reinstatement of alcohol seeking in Wistar rats, they found that L822429 attenuates yohimbine-induced reinstatement of alcohol seeking, but does not affect baseline alcohol self-administration. They observed a similar suppression of yohimbine-induced reinstatement of cocaine seeking by L822429, and found that Long-Evans rats exhibit greater sensitivity to NK1R antagonism than Wistar rats. Accordingly, Long-Evans rats exhibit differences in the expression of NK1Rs in some subcortical brain regions. Combined, these findings suggest that while NK1R antagonism differentially influences alcohol- and cocaine-related behavior, this receptor mediates stress-induced seeking of both drugs.

Differential Effects Of Opioid-Related Ligands and NSAIDs In Nonhuman Primate Models Of Acute and Inflammatory Pain. Sukhtankar DD, Lee H, Rice KC, Ko MC. Psychopharmacology (Berl). 2013, epub Nov 12, 2013.
Carrageenan-induced hyperalgesia is a widely used pain model in rodents. However, characteristics of carrageenan-induced hyperalgesia and effects of analgesic drugs under these conditions are unknown in nonhuman primates. The aims of this study were to develop carrageenan-induced hyperalgesia in rhesus monkeys and determine the efficacy and potency of agonists selective for the four opioid receptor subtypes in this model versus acute pain, as compared to non-steroidal anti-inflammatory drugs (NSAIDs). Tail injection of carrageenan produced long-lasting thermal hyperalgesia in monkeys. Systemically administered agonists selective for opioid receptor subtypes, i.e., fentanyl (mu/MOP), U-50488H (kappa/KOP), SNC80 (delta/DOP) and Ro 64-6198 (nociceptin/orphanin FQ/NOP) dose-dependently attenuated carrageenan-induced thermal hyperalgesia with different potencies. In absence of carrageenan, these agonists, except SNC80, blocked acute thermal nociception. Opioid-related ligands, especially Ro 64-6198, were much more potent for their antihyperalgesic than antinociceptive effects. Both effects were mediated by the corresponding receptor mechanisms. Only fentanyl produced scratching at antihyperalgesic and antinociceptive doses consistent with its pruritic effects in humans, illustrating a translational profile of MOP agonists in nonhuman primates. Similar to SNC80, systemically administered NSAIDs ketorolac and naproxen dose-dependently attenuated carrageenan-induced hyperalgesia but not acute nociception. Using two different pain modalities in nonhuman primates, effectiveness of clinically available analgesics like fentanyl, ketorolac and naproxen was distinguished and their efficacies and potencies were compared with the selective KOP, DOP, and NOP agonists. The opioid-related ligands displayed differential pharmacological properties in regulating hyperalgesia and acute nociception in the same subjects. Such preclinical primate models can be used to investigate novel analgesic agents.

Molecular Neurobiology Branch

Curious Cases: Altered Dose-Response Relationships In Addiction Genetics. Uhl GR, Drgonova J, Hall FS. Pharmacol Ther. 2013 Nov 1. doi:pii: S0163-7258(13)00218-0. 10.1016/j.pharmthera.2013.10.013. [Epub ahead of print] PMID: 24189489.
Dose-response relationships for most addictive substances are "inverted U"-shaped. Addictive substances produce both positive features that include reward, euphoria, anxiolysis, withdrawal-relief, and negative features that include aversion, dysphoria, anxiety and withdrawal symptoms. A simple model differentially associates ascending and descending limbs of dose-response curves with rewarding and aversive influences, respectively. However, Diagnostic and Statistical Manual (DSM) diagnoses of substance dependence fail to incorporate dose-response criteria and don't directly consider balances between euphoric and dysphoric drug effects. Classical genetic studies document substantial heritable influences on DSM substance dependence. Linkage and genome-wide association studies identify modest-sized effects at any locus. Nevertheless, clusters of SNPs within selected genes display 10-2>p>10-8 associations with dependence in many independent samples. For several of these genes, evidence for cis-regulatory, level-of-expression differences supports the validity of mouse models in which levels of expression are also altered. This review documents surprising, recently defined cases in which convergent evidence from humans and mouse models supports central influences of altered dose-response relationships in mediating the impact of relevant genomic variation on addiction phenotypes. For variation at loci for the α5 nicotinic acetylcholine receptor, cadherin 13, receptor type protein tyrosine phosphatase Δ and neuronal cell adhesion molecule genes, changed dose-response relationships conferred by gene knockouts in mice are accompanied by supporting human data. These observations emphasize desirability of carefully elucidating dose-response relationships for both rewarding and aversive features of abused substances wherever possible. They motivate consideration of individual differences in dose-response relationships in addiction nosology and therapeutics.

Reducing Aggression and Impulsivity Through School-Based Prevention Programs: A Gene By Intervention Interaction. Musci RJ, Bradshaw CP, Maher B, Uhl GR, Kellam SG, Ialongo NS. Prev Sci. 2013 Nov 1. [Epub ahead of print] PMID: 24178584.
A variety of school-based, universal preventive interventions have been developed to address behavioral and mental health problems. Unfortunately, few have been evaluated within the context of randomized controlled trials with long-term follow-up. Even fewer still have examined the potential genetic factors that may drive differential impact of the intervention. In the present analysis, the authors examine the extent to which the longitudinal effects of two elementary school-based interventions were moderated by the brain-derived neurotrophic factor (BDNF) gene, which has been linked with aggression and impulsive behaviors. The sample included 678 urban, primarily African American children who were randomly assigned along with their teachers to one of three first grade classroom conditions: classroom-centered (CC) intervention, Family School Partnership (FSP), or a control condition. The teacher ratings of the youth's aggressive and impulsive behavior were obtained at baseline and in grades 6-12. Single-nucleotide polymorphisms (SNPs) from the BDNF gene were extracted from the genome-wide data. Longitudinal latent trait-state-error models indicated a significant interaction between a particular profile of the BDNF SNP cluster (46 % of sample) and CC intervention on impulsivity (β=-.27, p<.05). A similar interaction was observed for the BDNF SNP cluster and the CC

intervention on aggression (β=-.14, p<.05). The results suggest that the impacts of preventive interventions in early elementary school on late adolescent outcomes of impulsivity and aggression can be potentially modified by genetic factors, such as BDNF.

Involvement of the Neutral Amino Acid Transporter SLC6A15 and Leucine In Obesity-Related Phenotypes. Drgonova J, Jacobsson JA, Han JC, Yanovski JA, Fredriksson R, Marcus C, Schiöth HB, Uhl GR. PLoS One. 2013 Sep 4;8(9):e68245. doi:10.1371/journal.pone.0068245. PMID: 24023709.

Brain pathways, including those in hypothalamus and nucleus of the solitary tract, influence food intake, nutrient preferences, metabolism and development of obesity in ways that often differ between males and females. Branched chain amino acids, including leucine, can suppress food intake, alter metabolism and change vulnerability to obesity. The SLC6A15 (v7-3) gene encodes a sodium-dependent transporter of leucine and other branched chain amino acids that is expressed by neurons in hypothalamus and nucleus of the solitary tract. The authors now report that SLC6A15 knockout attenuates leucine's abilities to reduce both: a) intake of normal chow and b) weight gain produced by access to a high fat diet in gender-selective fashions. They identify SNPs in the human SLC6A15 that are associated with body mass index and insulin resistance in males. These observations in mice and humans support a novel, gender-selective role for brain amino acid compartmentalization mediated by SLC6A15 in diet and obesity-associated phenotypes.

B(0)AT2 (SLC6A15) Is Localized To Neurons and Astrocytes and Is Involved In Mediating the Effect Of Leucine In the Brain. Hägglund MG, Roshanbin S, Löfqvist E, Hellsten SV, Nilsson VC, Todkar A, Zhu Y, Stephansson O, Drgonova J, Uhl GR, Schiöth HB, Fredriksson R. PLoS One. 2013;8(3):e58651. doi: 10.1371/journal.pone.0058651. Epub 2013 Mar 7. PMID:23505546.

The B(0)AT2 protein is a product of the SLC6A15 gene belonging to the SLC6 subfamily and has been shown to be a transporter of essential branched-chain amino acids. The authors aimed to further characterize the B(0)AT2 transporter in CNS, and to use Slc6a15 knock out (KO) mice to investigate whether B(0)AT2 is important for mediating the anorexigenic effect of leucine. They used the Slc6a15 KO mice to investigate the role of B(0)AT2 in brain in response to leucine and in particular the effect on food intake. Slc6a15 KO mice show lower reduction of food intake as well as lower neuronal activation in the ventromedial hypothalamic nucleus (VMH) in response to leucine injections compared to wild type mice. They also used RT-PCR on rat tissues, in situ hybridization and immunohistochemistry on mouse CNS tissues to document in detail the distribution of SLC6A15 on gene and protein levels. They showed that B(0)AT2 immunoreactivity is mainly neuronal, including localization in many GABAergic neurons and spinal cord motor neurons. B(0)AT2 immunoreactivity was also found in astrocytes close to ventricles, and co-localized with cytokeratin and diazepam binding inhibitor (DBI) in epithelial cells of the choroid plexus. The data suggest that B(0)AT2 play a role in leucine homeostasis in the brain. B(0)AT2 (SLC6A15) is localized to neurons and astrocytes, and is involved in mediating the effect of leucine in the brain.

Decreased Vesicular Monoamine Transporter 2 (VMAT2) and Dopamine Transporter (DAT) Function In Knockout Mice Affects Aging Of Dopaminergic Systems. Hall FS, Itokawa K, Schmitt A, Moessner R, Sora I, Lesch KP, Uhl GR. Neuropharmacology. 2014 Jan; 76 Pt A:146-55. doi: 10.1016/j.neuropharm.2013.07.031. Epub 2013 Aug 24. PMID: 23978383. Dopamine (DA) is accumulated and compartmentalized by the dopamine transporter (DAT; SLC3A6) and the vesicular monoamine transporter 2 (VMAT2; SLC18A2). These transporters work at the plasma and vesicular membranes of dopaminergic neurons, respectively, and thus regulate levels of DA in neuronal compartments that include the extravesicular cytoplasmic compartment. DA in this compartment has been hypothesized to contribute to oxidative damage that can reduce the function of dopaminergic neurons in aging brains and may contribute to reductions in dopaminergic neurochemical markers, locomotor behavior and responses to dopaminergic drugs that are found in aged animals. The studies reported here examined aged mice with heterozygous deletions of VMAT2 or of DAT, which each reduce transporter expression to about 50% of levels found in wild-type (WT) mice. Aged mice displayed reduced locomotor responses under a variety of circumstances, including in response to locomotor stimulants, as well as changes in monoamine levels and metabolites in a regionally dependent manner. Several effects of aging were more pronounced in heterozygous VMAT2 knockout (KO) mice, including aging induced reductions in locomotion and reduced locomotor responses to cocaine. By contrast, some effects of aging were reduced or not observed in heterozygous DAT KO mice. These findings support the idea that altered DAT and VMAT2 expression affect age-related changes in dopaminergic function. These effects are most likely mediated by alterations in DA compartmentalization, and might be hypothesized to be exacerbated by other factors that affect the metabolism of cytosolic DA. Decreased vesicular monoamine transporter 2 (VMAT2) and dopamine transporter (DAT) function in knockout mice affects aging of dopaminergic systems.

Implications Of Genome Wide Association Studies For Addiction: Are Our A Priori Assumptions All Wrong? Hall FS, Drgonova J, Jain S, Uhl GR. Pharmacol Ther. 2013 Dec; 140(3): 267-279. doi: 10.1016/j.pharmthera.2013.07.006. Epub 2013 Jul 18. PMID: 23872493. Substantial genetic contributions to addiction vulnerability are supported by data from twin studies, linkage studies, candidate gene association studies and, more recently, Genome Wide Association Studies (GWAS). Parallel to this work, animal studies have attempted to identify the genes that may contribute to responses to addictive drugs and addiction liability, initially focusing upon genes for the targets of the major drugs of abuse. These studies identified genes/proteins that affect responses to drugs of abuse; however, this does not necessarily mean that variation in these genes contributes to the genetic component of addiction liability. One of the major problems with initial linkage and candidate gene studies was an a priori focus on the genes thought to be involved in addiction based upon the known contributions of those proteins to drug actions, making the identification of novel genes unlikely. The GWAS approach is systematic and agnostic to such a priori assumptions. From the numerous GWAS now completed several conclusions may be drawn: (1) addiction is highly polygenic; each allelic variant contributing in a small, additive fashion to addiction vulnerability; (2) unexpected, compared to our a priori assumptions, classes of genes are most important in explaining addiction vulnerability; (3) although substantial genetic heterogeneity exists, there is substantial convergence of GWAS signals on particular genes. This review traces the history of this research; from initial transgenic mouse models based upon candidate gene and linkage studies,

through the progression of GWAS for addiction and nicotine cessation, to the current human and transgenic mouse studies post-GWAS.

The Selective M Opioid Receptor Antagonist B-Funaltrexamine Attenuates Methamphetamine-Induced Stereotypical Biting In Mice. Kitanaka J, Kitanaka N, Hall FS, Uhl GR, Fukushima Y, Sawai T, Watabe K, Kubo H, Takahashi H, Tanaka K, Nishiyama N, Tatsuta T, Morita Y, Takemura M. Brain Res. 2013 Jul 19; 1522: 88-98. doi: 10.1016/j.brainres.2013.05.027. Epub 2013 May 28. PMID: 23727404.
The authors investigated whether pretreatment with opioid receptor antagonists affected methamphetamine (METH)-induced stereotypy in mice. Pretreatment of male ICR mice with naloxone, a relatively non-selective opioid receptor antagonist, significantly attenuated the total incidence of METH-induced stereotypical behavior compared with saline vehicle-pretreated subjects. Furthermore, the distribution of METH-induced stereotypical behavior was affected by naloxone administration. Thus, METH-induced stereotypical sniffing and persistent locomotion were significantly increased by naloxone treatment while stereotypical biting was reduced. One way to interpret this pattern of effects is that pretreatment with naloxone appeared to produce a shift in the dose-response curve for METH. Thus, while the more intense forms of oral-facial stereotypies were reduced, increased persistent locomotion was observed in mice given naloxone followed by METH. The selective μ opioid receptor antagonist β-funaltrexamine, but not nor-binaltorphimine (a κ-selective antagonist) nor naltrindole (a δ-selective antagonist), mimicked the effect of naloxone. These observations suggest that opioid receptor antagonists may attenuate METH-induced stereotypical biting in mice via μ opioid receptors, and suggest that antagonism of this system may be a potential therapeutic approach to reducing some deleterious effects of METH use and perhaps in the treatment of some forms of self-injurious behavior. The selective μ opioid receptor antagonist β-funaltrexamine attenuates methamphetamine-induced stereotypical biting in mice.

Biomarkers For Smoking Cessation. Bough KJ, Lerman C, Rose JE, McClernon FJ, Kenny PJ, Tyndale RF, David SP, Stein EA, Uhl GR, Conti DV, Green C, Amur S.Clin Pharmacol Ther. 2013 Jun;93(6):526-38. doi: 10.1038/clpt.2013.57. Epub 2013 Mar 18. PMID: 23588313.
One way to enhance therapeutic development is through the identification and development of evaluative tools such as biomarkers. This review focuses on putative diagnostic, pharmacodynamic, and predictive biomarkers for smoking cessation. These types of biomarkers may be used to more accurately diagnose a disease, personalize treatment, identify novel targets for drug discovery, and enhance the efficiency of drug development. Promising biomarkers are presented across a range of approaches including metabolism, genetics, and neuroimaging. A preclinical viewpoint is also offered, as are analytical considerations and a regulatory perspective summarizing a pathway toward biomarker qualification.

Altered Reward Circuitry In the Norepinephrine Transporter Knockout Mouse. Gallagher JJ, Zhang X, Hall FS, Uhl GR, Bearer EL, Jacobs RE. PLoS One. 2013;8(3):e57597. doi: 10.1371/journal.pone.0057597. Epub 2013 Mar 4. PMID: 23469209.
Synaptic levels of the monoamine neurotransmitters dopamine, serotonin, and norepinephrine are modulated by their respective plasma membrane transporters, albeit with a few exceptions. Monoamine transporters remove monoamines from the synaptic cleft and thus influence the degree and duration of signaling. Abnormal concentrations of these neuronal transmitters are

implicated in a number of neurological and psychiatric disorders, including addiction, depression, and attention deficit/hyperactivity disorder. This work concentrates on the norepinephrine transporter (NET), using a battery of in vivo magnetic resonance imaging techniques and histological correlates to probe the effects of genetic deletion of the norepinephrine transporter on brain metabolism, anatomy and functional connectivity. MRS recorded in the striatum of NET knockout mice indicated a lower concentration of NAA that correlates with histological observations of subtle dysmorphisms in the striatum and internal capsule. As with DAT and SERT knockout mice, the authors detected minimal structural alterations in NET knockout mice by tensor-based morphometric analysis. In contrast, longitudinal imaging after stereotaxic prefrontal cortical injection of manganese, an established neuronal circuitry tracer, revealed that the reward circuit in the NET knockout mouse is biased toward anterior portions of the brain. This is similar to previous results observed for the dopamine transporter (DAT) knockout mouse, but dissimilar from work with serotonin transporter (SERT) knockout mice where Mn(2+) tracings extended to more posterior structures than in wildtype animals. These observations correlate with behavioral studies indicating that SERT knockout mice display anxiety-like phenotypes, while NET knockouts and to a lesser extent DAT knockout mice display antidepressant-like phenotypic features. Thus, the mainly anterior activity detected with manganese-enhanced MRI in the DAT and NET knockout mice is likely indicative of more robust connectivity in the frontal portion of the reward circuit of the DAT and NET knockout mice compared to the SERT knockout mice.

An Evaluation of the Serotonin System and Perseverative, Compulsive, Stereotypical, and Hyperactive Behaviors In Dopamine Transporter (DAT) Knockout Mice. Fox MA, Panessiti, MG, Hall FS, Uhl GR, Murphy DL. Psychopharmacology (Berl). 2013 Jun; 227(4): 685-695. doi: 10.1007/s00213-013-2988-x. PMID: 23417514.

Mice lacking the dopamine transporter (DAT) display major behavioral alterations that include hyperactivity, perseverative locomotor patterns, and reduced prepulse inhibition of the acoustic startle reflex. The objectives of this study were to investigate perseverative, compulsive, stereotypical, and hyperactive behaviors, as well as serotonin and its involvement with these behaviors, in DAT gene-altered mice. In the open field, mean turn angle and meandering were decreased in DAT knockout (DAT-KO) mice. DAT-KO mice displayed increased hyperactivity, increased velocity, less time immobile, and a failure to habituate over time in the open field unlike their DAT wildtype (DAT-WT) and heterozygous (DAT-HET) littermates. DAT-KO mice buried fewer marbles than DAT-WT and -HET mice in an assessment of compulsive-like behaviors, likely due to extreme hyperactivity and related inattention. Stereotypical head weaving was increased in untreated DAT-KO mice. Following administration of the 5-HT1A/7 agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), stereotypical head weaving and forepaw treading were increased more in DAT-KO mice than in DAT-WT or -HET mice. By contrast, head twitches induced by treatment with the 5-HT2A/2C agonist (±)-2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) were similar in mice of all three DAT genotypes. 5-HT1A autoreceptor function was intact in DAT-KO mice. Compared to DAT-WT mice, serotonin levels were increased in DAT-HET and -KO mice in frontal cortex and hippocampus, respectively, and serotonin turnover rates were increased ~30 % in the striatum of DAT-KO mice. These findings extend and confirm prior behavioral and biochemical characterization of DAT-KO mice. Hyperactivity, stereotypy, and perseverative behaviors are increased in these

mice, with brain-area specific increases in serotonin levels and serotonin turnover, and marked increases in postsynaptic 5-HT1A receptor-mediated stereotypic responses

Exclusive Expression of VMAT2 In Noradrenergic Neurons Increases Viability Of Homozygous VMAT2 Knockout Mice. Ohara A, Kasahara Y, Yamamoto H, Hata H, Kobayashi H, Numachi Y, Miyoshi I, Hall FS, Uhl GR, Ikeda K, Sora I. Biochem Biophys Res Commun. 2013 Mar 15; 432(3): 526-532. doi: 10.1016/j.bbrc.2013.02.014. PMID:23410751.
The vesicular monoamine transporter 2 (VMAT2) translocates monoamine neurotransmitters from the neuronal cytoplasm into synaptic vesicles. Since VMAT2-/- mice die within a few days of birth, it is difficult to analyze the detailed VMAT2 functions using these mice. In this study, the authors generated human VMAT2 transgenic mice that expressed VMAT2 in noradrenergic neurons with the aim to rescue the lethality of VMAT2 deletion. The expression of human VMAT2 in noradrenergic neurons extended the life of VMAT2-/- mice for up to three weeks, and these mice showed severe growth deficiency compared with VMAT2+/+ mice. These results may indicate that VMAT2 expressed in noradrenergic neurons has crucial roles in survival during the first several weeks after birth, and VMAT2 functions in other monoaminergic systems could be required for further extended survival. Although VMAT2 rescue in noradrenergic neurons did not eliminate the increased morbidity and lethality associated with VMAT2 deletion, the extension of the lifespan in VMAT2 transgenic mice will enable behavioral, pharmacological and pathophysiological studies of VMAT2 function.

Impaired Cliff Avoidance Reaction In Dopamine Transporter Knockout Mice. Yamashita M, Sakakibara Y, Hall FS, Numachi Y, Yoshida S, Kobayashi H, Uchiumi O, Uhl GR, Kasahara Y, Sora I. Psychopharmacology (Berl). 2013 Jun; 227(4 : 74174-9. doi: 10.1007/s00213-013-3009-9.. PMID: 23397052.
Impulsivity is a key feature of disorders that include attention-deficit/hyperactivity disorder (ADHD). The cliff avoidance reaction (CAR) assesses maladaptive impulsive rodent behavior. Dopamine transporter knockout (DAT-KO) mice display features of ADHD and are candidates in which to test other impulsive phenotypes. Impulsivity of DAT-KO mice was assessed in the CAR paradigm. For comparison, attentional deficits were also assessed in prepulse inhibition (PPI) in which DAT-KO mice have been shown to exhibit impaired sensorimotor gating. DAT-KO mice exhibited a profound CAR impairment compared to wild-type (WT) mice. As expected, DAT-KO mice showed PPI deficits compared to WT mice. Furthermore, the DAT-KO mice with the most impaired CAR exhibited the most severe PPI deficits. Treatment with methylphenidate or nisoxetine ameliorated CAR impairments in DAT-KO mice. These results suggest that DAT-KO mice exhibit impulsive CAR behavior that correlates with their PPI deficits. Blockade of monoamine transporters, especially the norepinephrine transporter (NET) in the prefrontal cortex (PFC), may contribute to pharmacological improvement of impulsivity in these mice.

Behavioral Neuroscience Branch

Neurocircuitry of Motivation Section

Synergistic Interaction Of Amphetamine, Environment and State In Seeking Behavior. Keller KL, Vollrath-Smith FR, Jafari M, Ikemoto S. Psychopharmacology (Berl). 2013 Oct 8. [Epub ahead of print]. PMID: 24101157.
Approach behavior is regulated by the brain integrating information about environment and body state. Psychoactive drugs interact with this process. The authors examined the extent to which caloric (i.e., food) restriction, amphetamine and lithium interact in potentiating locomotor activity and responding reinforced by visual stimulus (VS), a reward unrelated to energy homeostasis. Rats either had ad-libitum access to food or received daily rations that maintained 85-90% of their original body weights. Leverpressing turned on a cue light for 1 sec and turned off house light for 5 sec. Amphetamine and lithium were administered through intraperitoneal injections and diet, respectively. Food-restriction or amphetamine (1 mg/kg) alone had little effect on VS-reinforced responding; however, the combination of the two conditions markedly potentiated VS-reinforced responding (4-fold). Food restriction lasting 7 days or longer was needed to augment amphetamine's effect on VS-reinforced responding. Amphetamine (0.3 – 3 mg/kg) potentiated locomotor activity similarly between food-restricted and ad-libitum groups. Repeated injections of amphetamine sensitized locomotor activity, but not VS-reinforced responding. In addition, while chronic lithium treatments (0.2% lithium carbonate chow) reduced VS-reinforced responding, chronic lithium further augmented amphetamine-potentiated VS-reinforced responding. Food-restriction interacts with psychoactive drugs to potentiate goal-directed responding unrelated to food-seeking in a much more powerful manner than previously thought. The novel finding that lithium can augment a psychostimulant effect of amphetamine suggests caution when combining lithium and psychostimulant drugs in clinical settings.

Neurobiology of Relapse Section

Critical Role Of Peripheral Drug Actions In Experience-Dependent Changes In Nucleus Accumbens Glutamate Release Induced By Intravenous Cocaine. Wakabayashi KT, Kiyatkin EA. Journal of Neurochemistry. Oct 1, 2013. doi: 10.1111/jnc.12472. [Epub ahead of print].
Recent studies reveal that cocaine experience results in persistent neuroadaptive changes within glutamate (Glu) synapses in brain areas associated with drug reward. However, it remains unclear whether cocaine affects Glu release in drug-naive animals and how it is altered by drug experience. By using high-speed amperometry with enzyme-based and enzyme-free biosensors in freely moving rats, the authors show that an initial intravenous cocaine injection at a low self-administering dose (1 mg/kg) induces rapid, small and transient Glu release in the nucleus accumbens shell (NAc), which with subsequent injections rapidly becomes a much stronger, two-component increase. Using cocaine-methiodide, cocaine's analogue that does not cross the blood-brain barrier, the authors confirm that the initial cocaine-induced Glu release in the NAc has a peripheral neural origin. Unlike cocaine, Glu responses induced by cocaine-methiodide rapidly habituate following repeated exposure. However, after cocaine experience this drug induces cocaine-like Glu responses. Hence, the interoceptive actions of cocaine, which essentially precede its direct actions in the brain, play a critical role in experience-dependent

alterations in Glu release, cocaine-induced neural sensitization and may contribute to cocaine addiction.

Integrative Neuroscience Branch

Behavioral Neuroscience Section

Divergent Perspectives On Addiction. Wise, RA, Koob GF. Neuropsychopharmacology 2013, epub ahead of print.
What is the defining property of addiction? The authors dust off a several-decades-long debate about the relative importance of two forms of reinforcement—positive reinforcement, subjectively linked to drug-induced euphoria, and negative reinforcement, subjectively linked to the alleviation of pain—both of which figure importantly in addiction theory; each of these forms has dominated addiction theory in its time. The authors agree that addiction begins with the formation of habits through positive reinforcement and that drug-opposite physiological responses often establish the conditions for negative reinforcement to come into play at a time when tolerance, in the form of increasing reward thresholds, appears to develop into positive reinforcement. Wise's work has tended to focus on positive-reinforcement mechanisms that are important for establishing drug-seeking habits and reinstating them quickly after periods of abstinence, whereas Koob's work has tended to focus on the negative-reinforcement mechanisms that become most obvious in the late stages of sustained addiction. While the authors tend to agree with each other about the early and late stages of addiction, they hold different views as to (i) the point between early and late at which the diagnosis of 'addiction' should be invoked, (ii) the relative importance of positive and negative reinforcement leading up to this transition, and (iii) the degree to which the specifics of negative reinforcement can be generalized across the range of addictive agents.

Behavioral Neuroscience Research Branch

Preclinical Pharmacology Section

Powerful Cocaine-Like Actions Of 3,4-Methylenedioxypyrovalerone (MDPV), A Principal Constituent Of Psychoactive 'Bath Salts' Products. Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, Holy M, Rothman RB, Goldberg SR, Lupica CR, Sitte HH, Brandt SD, Tella SR, Cozzi NV, Schindler CW. Neuropsychopharmacology 2013; 38(4): 552-562.
The abuse of psychoactive 'bath salts' containing cathinones such as 3,4-methylenedioxy-pyrovalerone (MDPV) is a growing public health concern, yet little is known about their pharmacology. Here, the authors evaluated the effects of MDPV and related drugs using molecular, cellular, and whole-animal methods. In vitro transporter assays were performed in rat brain synaptosomes and in cells expressing human transporters, while clearance of endogenous dopamine was measured by fast-scan cyclic voltammetry in mouse striatal slices. Assessments of in vivo neurochemistry, locomotor activity, and cardiovascular parameters were carried out in rats. The authors found that MDPV blocks uptake of [(3)H]dopamine (IC(50)=4.1 nM) and [(3)H]norepinephrine (IC(50)=26nM) with high potency but has weak effects on uptake of

[(3)H]serotonin (IC(50)=3349nM). In contrast to other psychoactive cathinones (eg, mephedrone), MDPV is not a transporter substrate. The clearance of endogenous dopamine is inhibited by MDPV and cocaine in a similar manner, but MDPV displays greater potency and efficacy. Consistent with in vitro findings, MDPV (0.1-0.3mg/kg, intravenous) increases extracellular concentrations of dopamine in the nucleus accumbens. Additionally, MDPV (0.1-3.0mg/kg, subcutaneous) is at least 10 times more potent than cocaine at producing locomotor activation, tachycardia, and hypertension in rats. These data show that MDPV is a monoamine transporter blocker with increased potency and selectivity for catecholamines when compared with cocaine. The robust stimulation of dopamine transmission by MDPV predicts serious potential for abuse and may provide a mechanism to explain the adverse effects observed in humans taking high doses of 'bath salts' preparations.

Reducing Cannabinoid Abuse and Preventing Relapse By Enhancing Endogenous Brain Levels Of Kynurenic Acid. Justinova Z, Mascia P, Wu HQ, Secci ME, Redhi GH, Panlilio LV, Scherma M, Barnes C, Parashos A, Zara T, Fratta W, Solinas M, Pistis M, Bergman J, Kangas BD, Ferré S, Tanda G, Schwarcz R, Goldberg SR. Nature Neuroscience 2013; 16(11): 1652-1661.

In the reward circuitry of the brain, α-7-nicotinic acetylcholine receptors (α7nAChRs) modulate effects of Δ(9)-tetrahydrocannabinol (THC), marijuana's main psychoactive ingredient. Kynurenic acid (KYNA) is an endogenous negative allosteric modulator of α7nAChRs. Here the authors report that the kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 increases brain KYNA levels and attenuates cannabinoid-induced increases in extracellular dopamine in reward-related brain areas. In the self-administration model of drug abuse, Ro 61-8048 reduced the rewarding effects of THC and the synthetic cannabinoid WIN 55,212-2 in squirrel monkeys and rats, respectively, and it also prevented relapse to drug-seeking induced by reexposure to cannabinoids or cannabinoid-associated cues. The effects of enhancing endogenous KYNA levels with Ro 61-8048 were prevented by positive allosteric modulators of α7nAChRs. Despite a clear need, there are no medications approved for treatment of marijuana dependence. Modulation of KYNA offers a pharmacological strategy for achieving abstinence from marijuana and preventing relapse.

Neuroimaging Research Branch

Acute Nicotine Differentially Impacts Anticipatory Valence- and Magnitude-Related Striatal Activity. Ros EJ, Ross TJ, Salmeron BJ, Lee M, Shakleya DM, Huestis MA, Stein EA. Biological Psychiatry 2013; 73: 280-288.

Dopaminergic activity plays a role in mediating the rewarding aspects of abused drugs, including nicotine. Nicotine modulates the reinforcing properties of other motivational stimuli, yet the mechanisms of this interaction are poorly understood. This study aimed to ascertain the impact of nicotine exposure on neuronal activity associated with reinforcing outcomes in dependent smokers. Smokers (n = 28) and control subjects (n = 28) underwent functional imaging during performance of a monetary incentive delay task. Using a randomized, counterbalanced design, smokers completed scanning after placement of a nicotine or placebo patch; nonsmokers were scanned twice without nicotine manipulation. In regions along dopaminergic pathway trajectories, the authors considered event-related activity for valence (reward/gain vs.

punishment/loss), magnitude (small, medium, large), and outcome (successful vs. unsuccessful). Both nicotine and placebo patch conditions were associated with reduced activity in regions supporting anticipatory valence, including ventral striatum. In contrast, relative to controls, acute nicotine increased activity in dorsal striatum for anticipated magnitude. Across conditions, anticipatory valence-related activity in the striatum was negatively associated with plasma nicotine concentration, whereas the number of cigarettes daily correlated negatively with loss anticipation activity in the medial prefrontal cortex only during abstinence. These data suggest a partial dissociation in the state- and trait-specific effects of smoking and nicotine exposure on magnitude- and valence-dependent anticipatory activity within discrete reward processing brain regions. Such variability may help explain, in part, nicotine's impact on the reinforcing properties of nondrug stimuli and speak to the continued motivation to smoke and cessation difficulty.

Intrinsic Resting State Activity Predicts Working Memory Brain Activation and Behavioral Performance. Zou Q, Ross TJ, Gu H, Geng X, Zuo X-N, Hong LE, Stein EA, Zang Y, Yang Y. Human Brain Mapping 2013; 34: 3204-3215.
Although resting-state brain activity has been demonstrated to correspond with task-evoked brain activation, the relationship between intrinsic and evoked brain activity has not been fully characterized. For example, it is unclear whether intrinsic activity can also predict task-evoked deactivation and whether the rest-task relationship is dependent on task load. In this study, the authors addressed these issues on 40 healthy control subjects using resting-state and task-driven [N-back working memory (WM) task] functional magnetic resonance imaging data collected in the same session. Using amplitude of low-frequency fluctuation (ALFF) as an index of intrinsic resting-state activity, we found that ALFF in the middle frontal gyrus and inferior/superior parietal lobules was positively correlated with WM task-evoked activation, while ALFF in the medial prefrontal cortex, posterior cingulate cortex, superior frontal gyrus, superior temporal gyrus, and fusiform gyrus was negatively correlated with WM task-evoked deactivation. Further, the relationship between the intrinsic resting-state activity and task-evoked activation in lateral/superior frontal gyri, inferior/superior parietal lobules, superior temporal gyrus, and midline regions was stronger at higher WM task loads. In addition, both resting-state activity and the task-evoked activation in the superior parietal lobule/precuneus were significantly correlated with the WM task behavioral performance, explaining similar portions of intersubject performance variance. Together, these findings suggest that intrinsic resting-state activity facilitates or is permissive of specific brain circuit engagement to perform a cognitive task, and that resting activity can predict subsequent task-evoked brain responses and behavioral performance.

Prefrontal White Matter Impairment In Substance Users Depends Upon The Catechol-O-Methyl Transferase (COMT) Val158met Polymorphism. Zhang X, Lee MR, Salmeron BJ, Stein DL, Hong LE, Geng X, Ross TJ, Wang Y, Hodgkinson C, Shen P-H, Yang Y, Goldman D, Stein EA. NeuroImage 2013; 69: 62-69.
Individuals addicted to most chemical substances present with hypoactive dopaminergic systems as well as altered prefrontal white matter structure. Prefrontal dopaminergic tone is under genetic control and is influenced by and modulates descending cortico-striatal glutamatergic pathways that in turn, regulate striatal dopamine release. The catechol-O-methyltransferase (COMT) gene contains an evolutionarily recent and common functional variant at codon 108/158 (rs4680) that plays an important role in modulating prefrontal dopaminergic tone. To determine if the COMT

val158met genotype influences white matter integrity (i.e., fractional anisotropy (FA)) in substance users, 126 healthy controls and 146 substance users underwent genotyping and magnetic resonance imaging. A general linear model with two between-subjects factors (COMT genotype and addiction status) was performed using whole brain diffusion tensor imaging (DTI) to assess FA. A significant Genotype × Drug Use status interaction was found in the left prefrontal cortex. Post-hoc analysis showed reduced prefrontal FA only in Met/Met homozygotes who were also drug users. These data suggest that Met/Met homozygous individuals, in the context of addiction, have increased susceptibility to white matter structural alterations, which might contribute to previously identified structural and functional prefrontal cortical deficits in addiction.

Large-Scale Brain Networks In the Awake, Truly Resting Marmoset Monkey. Belcher AM, Yen CC, Stepp H, Gu H, Lu H, Yang Y, Silva AC, Stein, EA. Journal of Neuroscience 2013; 33: 16796-16804.
Resting-state functional MRI is a powerful tool that is increasingly used as a noninvasive method for investigating whole-brain circuitry and holds great potential as a possible diagnostic for disease. Despite this potential, few resting-state studies have used animal models (of which nonhuman primates represent our best opportunity of understanding complex human neuropsychiatric disease), and no work has characterized networks in awake, truly resting animals. Here the authors present results from a small New World monkey that allows for the characterization of resting-state networks in the awake state. Six adult common marmosets (Callithrix jacchus) were acclimated to light, comfortable restraint using individualized helmets. Following behavioral training, resting BOLD data were acquired during eight consecutive 10 min scans for each conscious subject. Group independent component analysis revealed 12 brain networks that overlap substantially with known anatomically constrained circuits seen in the awake human. Specifically, the authors found eight sensory and "lower-order" networks (four visual, two somatomotor, one cerebellar, and one caudate-putamen network), and four "higher-order" association networks (one default mode-like network, one orbitofrontal, one frontopolar, and one network resembling the human salience network). In addition to their functional relevance, these network patterns bear great correspondence to those previously described in awake humans. This first-of-its-kind report in an awake New World nonhuman primate provides a platform for mechanistic neurobiological examination for existing disease models established in the marmoset.

Withdrawal From Long-Term Methamphetamine Self-Administration 'Normalizes' Neurometabolites In Rhesus Monkeys: A 1H MR Spectroscopy Study. Yang S, Belcher A, Chefer S, Vaupel DB, Schindler C, Stein EA, Yang Y. Addiction Biology 2013 Aug 4. doi: 10.1111/adb.12078. [Epub ahead of print].
1 H magnetic resonance spectroscopy has demonstrated alterations in several neurometabolites in methamphetamine (METH)-dependent individuals in brain regions implicated in addiction. Yet, it is unclear whether these neurochemicals return to homeostatic levels after an individual abstains from drug use, a difficult question to address due to high recidivism and poor study retention in human subjects. The authors thus utilized a non-human primate model of addiction to explore the effects of long-term drug exposure and withdrawal on brain neurochemistry. Ten rhesus macaque monkeys on an active METH self-administration protocol (average use 4.6±0.8 years, average daily intake between 0.4 and 1.2mg/kg) and 10 age- and sex-matched drug-naive

controls (CONT) served as subjects. Concentrations of several neurochemicals were evaluated at several timepoints following withdrawal from drug availability (10 monkeys at 1 week and 1 and 3 months, and 6 monkeys at 6 and 12 months; CONT examined at one timepoint). At 1 week following METH withdrawal, the authors found increases in myo-inositol in anterior cingulate cortex in the METH group relative to CONT. These alterations showed a linear pattern of decreased levels ('normalization') by 1 year of abstinence. Thew authors also found decreases in glutamine and Glx (composed mainly of glutamate and glutamine) in the caudate-putamen of the same animals at early withdrawal that showed a similar linear pattern of increasing concentration by 1 year. These results demonstrate that despite protracted, long-term use, neurochemical changes seen following long-term drug administration do not persist following prolonged abstinence, suggesting therapeutic effects of long-term withdrawal from drug use.

Striatal-Insula Circuits In Cocaine Addiction: Implications For Impulsivity and Relapse Risk. McHugh MJ, Demers CH, Braud J, Briggs R Adinoff B, Stein EA. American Journal of Drug and Alcohol Abuse 2013; 39: 424-432.
Dysregulated striatal functioning coupled with executive control deficits arising from abnormal frontal cortical function are considered key mechanisms in the development and maintenance of cocaine addiction. The same features are thought to underlie high trait impulsivity observed in cocaine-addicted populations. Employing resting state functional connectivity, the current study sought to identify cortico-striatal circuit alterations in cocaine addiction and examine the degree to which circuit connectivity contributes to relapse risk and impulsivity among cocaine-addicted individuals. Whole-brain resting-state functional magnetic resonance imaging connectivity was assessed in 45 cocaine-addicted individuals relative to 22 healthy controls using seed volumes in the left and right caudate, putamen and nucleus accumbens. Cocaine-addicted individuals completed scans in the final week of a 2-4 weeks residential treatment episode. Relapse by day 30 post-discharge served to separate cocaine-addicted individuals into relapse and non-relapse groups. All participants completed the Barratt Impulsivity Scale (BIS-11a). Cocaine-addicted individuals exhibited reduced positive connectivity between the bilateral putamen and posterior insula and right postcentral gyrus. Group differences were primarily driven by reduced connectivity in relapse individuals relative to controls. No relapse versus non-relapse differences emerged. Impulsivity (BIS-11a) was higher in cocaine-addicted participants, an effect that was partially mediated by reduced putamen-posterior insula connectivity in this group. Cocaine addiction, relapse risk and impulsivity were associated with reduced connectivity in putamen-posterior insula/postcentral gyrus circuits implicated in temporal discounting and habitual responding. Findings provide new insight into the neurobiological mechanisms underlying impulsivity and relapse in cocaine addiction.

Acute Nicotine Administration Effects On Fractional Anisotropy Of Cerebral White Matter and Associated Attention Performance. Kochunov P, Du X, Moran L, Sampath H, Wijtenburg SA, Yang Y, Rowland LM, Stein EA, Hong LE. Frontiers in Pharmacology 4:117.doi: 10.3389/fphar.2013.00117, 2013.
Nicotinic acetylcholine receptors are present in the cerebral white matter (WM). The authors hypothesized that WM response to nicotine can be detected by diffusion tensor imaging (DTI); and that such responses may be associated with nicotine-led cognitive enhancement in sustained attention. A randomized, nicotine-placebo patch, crossover, double-blind clinical trial in two non-overlapping cohorts of smokers was used to test the hypothesis. The discovery cohort

consisted of 39 subjects (N = 20/19 controls/schizophrenic patients, age = 36.8 ± 10.1 years) and the replication cohorts consisted of 38 healthy smokers (31.7 ± 10.5 years). WM integrity was measured by fractional anisotropy (FA) values for the whole brain and nine preselected WM tracts using tract-based-spatial-statistics. Nicotine significantly enhanced FA values for the genu of corpus callosum compared with placebo (ΔFAgenu) ($p = 0.01$) in smokers with low recent smoking exposure as measured by low average cotinine level. This finding was replicated in the second cohort ($p = 0.02$). ΔFAgenu values explained 22% of variance in performance of a sustained attention task during the nicotine session ($p = 0.006$). However, this effect was limited to schizophrenia patients ($r = 0.62$ and 0.09; $p = 0.003$ and 0.7 for patients and controls, respectively). Acute pharmacological influence of nicotine patch on WM integrity appeared present, but was dependent on nicotine intake from recent smoking. Change in the WM integrity in the genu of corpus callosum was associated with a significant proportion of variability of nicotine-led changes in sustained attention/working memory of the smokers. Further studies will be necessary to understand biophysical underpinning of the nicotine-related changes in FA.

Resting State Functional Connectivity: A Review Of Its Physiological Bases and Applications In Neuropharmacology. Lu H, Stein EA. Neuropharmacology 2013 Sep 4. doi:pii: S0028-3908(13)00390-0. 10.1016/j.neuropharm.2013.08.023. [Epub ahead of print] 2013.

Brain structures do not work in isolation; they work in concert to produce sensory perception, motivation and behavior. Systems-level network activity can be investigated by resting state magnetic resonance imaging (rsMRI), an emerging neuroimaging technique that assesses the synchrony of the brain's ongoing spontaneous activity. Converging evidence reveals that rsMRI is able to consistently identify distinct spatiotemporal patterns of large-scale brain networks. Dysregulation within and between these networks has been implicated in a number of neurodegenerative and neuropsychiatric disorders, including Alzheimer's disease and drug addiction. Despite wide application of this approach in systems neuroscience, the physiological basis of these fluctuations remains incompletely understood. Here the authors review physiological studies in electrical, metabolic and hemodynamic fluctuations that are most pertinent to the rsMRI signal. They also review recent applications to neuropharmacology - specifically drug effects on resting state fluctuations. They speculate that the mechanisms governing spontaneous fluctuations in regional oxygenation availability likely give rise to the observed rsMRI signal. They conclude by identifying several open questions surrounding this technique.

Factors Modulating Neural Reactivity To Drug Cues In Addiction: A Survey Of Human Neuroimaging Studies. Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov, Y. Neuroscience & Biobehavioral Reviews. 2013 Nov 6. doi:pii: S0149-7634(13)00247-9. 10.1016/j.neubiorev.2013.10.013. [Epub ahead of print].

Human neuroimaging studies suggest that neural cue reactivity is strongly associated with, indices of drug use, including addiction severity and treatment success. However, little is known about, factors that modulate cue reactivity. The goal of this review, in which the authors survey published fMRI and, PET studies on drug cue reactivity in cocaine, alcohol, and tobacco cigarette users, is to highlight major, factors that modulate brain reactivity to drug cues. First, they describe cue reactivity paradigms used in, neuroimaging research and outline the brain circuits that underlie cue reactivity. They then discuss, major factors that have been shown to

modulate cue reactivity and review specific evidence as well as, outstanding questions related to each factor. Building on previous model-building reviews on the topic, they then outline a simplified model that includes the key modulatory factors and a tentative ranking of, their relative impact. The authors conclude with a discussion of outstanding challenges and future research, directions, which can inform future neuroimaging studies as well as the design of treatment and, prevention programs.

MR Imaging and Spectroscopy Section

Resting-State Glutamate and GABA Concentrations Predict Task-Induced Deactivation In The Default Mode Network. Hu Y, Chen X, Gu H, Yang Y. J. Neuroscience 33:18566-18573, 2013.
Deactivation of the human brain's default mode network (DMN) is regarded as suppression of endogenous activity to support exogenous task-related processes. This phenomenon has important functional relevance and insufficient DMN deactivation has been implicated in several neuropsychiatric disorders. However, the neurochemical mechanism of the DMN's deactivation remains largely unknown. In the present study, the authors test the hypothesis that the major excitatory and inhibitory neurotransmitters, glutamate and GABA, respectively, are associated with DMN deactivation. They used magnetic resonance spectroscopy to measure neurotransmitter concentrations in the posterior cingulate cortex/precuneus (PCC/PCu), a key component of the DMN, and functional magnetic resonance imaging to evaluate DMN deactivation induced by an n-back working memory task. Their results demonstrate significant associations of glutamate and GABA with DMN deactivation. Specifically, high regional GABA concentration in the PCC/PCu area is associated with enhanced deactivation induced by the task in the same region, whereas high glutamate concentration is associated with reduced deactivation. Furthermore, the association between GABA and DMN deactivation increases with the cognitive loads. These neurochemical characteristics of DMN deactivation may provide novel insights toward better understanding of the DMN's functions under normal physiological conditions and dysfunction in neuropsychiatric disorders.

Detecting Resting-State Brain Activity By Spontaneous Cerebral Blood Volume Fluctuations Using Whole Brain Vascular Space Occupancy Imaging. Miao X, Gu H, Yan L, Lu H, Wang DJ, Zhou XJ, Zhuo Y, Yang Y. NeuroImage 2014; 84: 575-584.
Resting-state brain activity has been investigated extensively using BOLD contrast. However, BOLD signal represents the combined effects of multiple physiological processes and its spatial localization is less accurate than that of cerebral blood flow and volume (CBF and CBF, respectively). In this study, the authors demonstrate that resting-state brain activity can be reliably detected by spontaneous fluctuations of CBV-weighted signal using whole-brain gradient and spin echo (GRASE) based vascular space occupancy (VASO) imaging. Specifically, using independent component analysis, intrinsic brain networks, including default mode, salience, executive control, visual, auditory, and sensorimotor networks were revealed robustly by the VASO technique. The authors further demonstrate that task-evoked VASO signal aligned well with expected gray matter areas, while blood-oxygenation level dependent (BOLD) signal extended outside of these areas probably due to their different spatial specificity. The improved spatial localization of VASO is consistent with previous studies using animal models.

Moreover, the authors showed that the 3D-GRASE VASO images had reduced susceptibility-induced signal voiding, compared to the BOLD technique. This is attributed to the fact that VASO does not require T2* weighting, thus the acquisition can use a shorter TE and can employ spin-echo scheme. Consequently VASO-based functional connectivity signals were well preserved in brain regions that tend to suffer from signal loss and geometric distortion in BOLD, such as orbital prefrontal cortex. This study suggests that 3D-GRASE VASO imaging, with its improved spatial specificity and less sensitivity to susceptibility artifacts, may have advantages in resting-state fMRI studies.

Cellular Neurobiology Research Branch

Behavioral Neurophysiology Research Section

Disruption Of Model-Based Behavior and Learning By Cocaine Self-Administration In Rats. Wied HM, Jones JL, Cooch NK, Berg BA, Schoenbaum, G. Psychopharmacology 2013; 229: 493-501. doi: 10.1007/s00213-013-3222-6.

Addiction is characterized by maladaptive decision-making, in which individuals seem unable to use adverse outcomes to modify their behavior. Adverse outcomes are often infrequent, delayed, and even rare events, especially when compared to the reliable rewarding drug-associated outcomes. As a result, recognizing and using information about their occurrence put a premium on the operation of so-called model-based systems of behavioral control, which allow one to mentally simulate outcomes of different courses of action based on knowledge of the underlying associative structure of the environment. This suggests that addiction may reflect, in part, drug-induced dysfunction in these systems. Here, the authors tested this hypothesis. This study aimed to test whether cocaine causes deficits in model-based behavior and learning independent of requirements for response inhibition or perception of costs or punishment. The authors trained rats to self-administer sucrose or cocaine for 2 weeks. Four weeks later, the rats began training on a sensory preconditioning and inferred value blocking task. Like devaluation, normal performance on this task requires representations of the underlying task structure; however, unlike devaluation, it does not require either response inhibition or adapting behavior to reflect aversive outcomes. Rats trained to self-administer cocaine failed to show conditioned responding or blocking to the preconditioned cue. These deficits were not observed in sucrose-trained rats nor did they reflect any changes in responding to cues paired directly with reward. These results imply that cocaine disrupts the operation of neural circuits that mediate model-based behavioral control.

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

RECEIPT, REFERRAL, AND REVIEW

- Total # of grant applications: 1,301
- DA primary: 923
- Institute-based reviews (Seventeen Grants and five Contracts reviews)

GRANT REVIEWS

PAR-13-084 and **PAR-10-227**: **PAR-13-084**: NIDA Research Education Program for Clinical Researchers and Clinicians (R25); **PAR-10-227**: Science Education Drug Abuse Partnership Award (R25)

PA-11-184 (T32): Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants

PA13-118: Multisite Clinical Trials

PAR-12-066 (R03): NIDA I/START Small Grant Review

PAR12-279 (R34): HIV/AIDS and Substance Abuse

PAS-12-122 (R01): Strategic Alliances for Medications Development to Treat Substance Use Disorders (R01)

PA12-212 (R13): R13 Conference Grant Review (PA12-212)

PAR-11-109 (U01): Grand Opportunity in Medications Development for Substance-Related Disorders (U01)

RFA-DA-14-003 (R01): Advancing Exceptional Research on HIV/AIDS (Avant-Garde)

PAR-12-086 (R21): Cutting-Edge Basic Research Awards (CEBRA) (R21)

RFA-DA-14-004 (U54): Medications Development Centers of Excellence Cooperative Program

RFA-DA-14-005 (R01); **RFA-DA-14-006 (R21)**: Substance Use Disorders and Molecular Regulation of Brain Energy Utilization (R01) (R21)

RFA-DA-14-007 (U01): Seek, Test, Treat, and Retain Data Harmonization Coordinating Center

PAR-12-199 (R25): Research Education Grants for Statistical and Computational Training in the Genetics of Addiction (R25)

PAR-11-060 (R24): DIDARP R24: Diversity-promoting Institutions Drug Abuse Research Program (DIDARP) (R24)

PAR-13-084 and **PAR-10-227 (AIDS)**: SEP for R25 and T32 AIDS applications

RFA-DA-14-014 (R01): Revision Applications to Promote Collaborative Research on Addiction at NIH (CRAN): Comorbidity-Related Research

CONTRACT REVIEWS

N01DA-14-8913: Assessment of Potential Cocaine Treatment in Non-Human Primates (8913)

N01DA-14-7788: Quantification of Drugs of Abuse and Related Substances in Biological Specimens

N01DA-14-5576: Concept review: National Addiction and HIV Data Archive Program (NAHDAP)

N01DA-14-4422: Concept review: NIH Pain Consortium Centers of Excellence in Pain Education

N01DA-14-1152: Concept review: NIDAMED; Outreach and Education to Health Care Providers on Substance Use (1152)

CERTIFICATES OF CONFIDENTIALITY

Between September 4 and December 5, 2013 OEA processed 51 Certificate of Confidentiality applications.

STAFF TRAINING AND DEVELOPMENT

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations.

Dr. Scott Chen, OEA, was selected to serve on the Presidential Management Fellows (PMF) Subcommittee of the NIH Administrative Training Committee (ATC). Members of the PMF Subcommittee typically meet monthly to plan and coordinate activities, including recruitment, for the PMF program. The PMF program provides a broad range of positions in administrative and program areas to high-potential aspiring leaders who have recently finished their degree in higher education. NIH has been hiring At-Large and Designated PMFs since 1985 to meet its long-term succession planning needs.

Dr. Scott Chen was chosen as a volunteer Board member and VP of Programs for the Project Management Institute Montgomery County MD Chapter, co-organized and –hosted a two-day project management training symposium October 17-18, 2013, that covered a wide range of topics, including project risks, agile project management, project cost benchmarking and modeling, front-end strategy, and leadership. There were over 300 attendees each day. Held at the Universities at Shady Grove campus, Bldg II.

Dr. Nadine Rogers, OEA, NIDA's Certificate of Confidentiality Coordinator, attended the Advancing Ethical Research Conference in Boston, MA from November 7-9, where she served as a table facilitator during a large group discussion of Roberto D'Abadie's , "The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects."

Dr. Jose Ruiz, OEA, was invited to participate in the NIDA Special Populations Research Development Seminar Series Workshop. He gave a presentation entitled, "Overview of the NIH Peer Review Process and Electronic Submission." The event was held on September 19-20, 2013 in Bethesda, MD.

CTN-RELATED REVIEW ACTIVITIES

The CTN Data and Safety Monitoring Board(s) met:

- August 28. 2013, to discuss final study results of protocol CTN 0052, A Randomized Controlled Trial of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence (BRAC).
- September 12, 2013, to discuss progress of protocol CTN 0049, Project HOPE–Hospital Visits as Opportunity for Prevention and Engagement for HIV Infected Drug Users.
- October 22, 2013, to discuss final study results of protocol CTN 0047, Screening, Motivational Assessment and Referral to Treatment in Emergency Departments (SMART-ED): Evaluation of Screening, Brief Intervention, Referral to Treatment and Booster Session for Drug Use Patients Presenting for Treatment in the Emergency Department.
  The Board also reviewed protocol CTN 0057-Ot, Screening, Brief Intervention, and Referral to Treatment in Primary Care (SBIRT-PC): An Add-on Project to Duke University Southeastern Diabetes Initiative.
- November 1, 2013, to discuss final study results of protocol CTN 0037, Stimulant Reduction Intervention using Dosed Exercise (STRIDE)
- November 26, 2013, to review protocol CTN 0059, The TAPS Tool: Screen and Brief Assessment Tool Validation Study
- December 16, 2013, to discuss final study results of protocol CTN 0048, Cocaine Use Reduction with Buprenorphine (CURB)

CONGRESSIONAL AFFAIRS SECTION
(Prepared January 22, 2014)

APPROPRIATIONS

Recently-signed legislation will fund NIH and NIDA for the balance of FY 2014. As described by the Congress, the bill includes $29.9 billion for the NIH, $1 billion above the fiscal year 2013 level. This funding will continue support for basic biomedical research and translational research through the programs like the Clinical and Translational Science Awards (CTSA) and Institutional Development Award (IDeA) to support scientists as they conduct research to discover cures. Further, it provides full support for the NIH Office of Science Education and programs like the Science Education and Partnership Awards (SEPA) to support biomedical research for the future.

Within the NIH amount, NIDA will receive an appropriation of $1,025,435,000. This represents an approximate increase of 3.2% above the FY 2013 "actuals" level of $993,403,793. Further, the Congress showed that it is focused on some drug abuse and addiction issues. In the statement of the managers, there is NIDA-specific language regarding research on opioids, medications development etc:

> *Opioid Drug Abuse* -- Opioid narcotics are frequently abused through injection, inhalation, crushing, or oral overdose to create a highly addictive euphoria. According to some reports, more than 35 million Americans have abused prescription opioids at some point in their lifetimes. In addition, the June 2011 Institute of Medicine report on relieving pain indicates that such abuse and misuse resulted in an annual estimated cost to the nation of $72.5 billion. The National Institute of Drug Abuse (NIDA) is expected to support meritorious scientific activities that provide companies with the basic science to develop and implement innovative strategies to reduce opioid drug abuse. Such strategies may include new chemical molecule structures, coatings, agents, or other appropriate scientifically sound processes with a goal of providing barriers to abuse while still providing the pain relief necessary for appropriate patient care. The NIDA is strongly urged to continue its support of research on pain, including the development of pain medications with reduced abuse liability. In addition, NIDA should continue to fund research to better prevent and treat prescription drug abuse. The NIDA shall provide an update in the fiscal year 2015 budget request on activities related to addressing the opioid drug abuse problem.

CONGRESSIONAL HEARINGS/MEETINGS

Synthetic Drugs Hearing -- On September 25, 2013, the Senate Caucus on International Narcotics Control held a hearing on "Dangerous Synthetic Drugs." NIDA Director Dr. Nora Volkow was one of the witnesses who testified. According to the Caucus, "The hearing examined the impact of dangerous synthetic drugs, such as Molly, K2, Spice and so-called "bath salts" and ways in which drug traffickers are circumventing existing law. Senator Feinstein recently introduced the Protecting Our Youth from Dangerous Synthetic Drugs Act of 2013 to combat synthetic drugs designed to mimic the effects of controlled substances like ecstasy, PCP and LSD, as well as THC, the principal chemical in marijuana. These controlled substance analogues are currently inadequately controlled under existing federal drug laws." All testimonies and an archived video file of the hearing can be seen at *http://www.drugcaucus.senate.gov/hearings.html.*

Treatment Medications – On September 30, 2013, the American Society of Addiction Medicine hosted a Congressional Briefing titled *Advancing Access to Addiction Treatment Medications*. Dr. Jack Stein, the Director of NIDA's Office of Science Policy and Communications, was one of the panelists focusing on this important topic. More information on the briefing can be found at *http://www.asam.org/advocacy/aaam/hill-briefing.*

SOME BILLS OF INTEREST

HR 486 – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

HR 498 – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. Representatives Rosa DeLauro (D-CT), and Frank Wolf (R-VA) were the only two original co-sponsors of the legislation. The bill was referred to the House Committee on Energy and Commerce.

HR 499 – On February 5, 2013, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

HR 672 -- On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

HR 1263 – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

HR 1285 – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary, and Judiciary. See also S 621. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

HR 1366 – On March 21, 2013, Representative Stephen Lynch (D-MA) introduced the Stop Oxycontin Abuse Act of 2013, to direct the Commissioner of Food and Drugs to modify the approval of any drug containing controlled-release oxycodone hydrochloride to limit such

approval to use for the relief of severe-only instead of moderate-to-severe pain, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

HR 1523 – On April 12, 2013, Representative Dana Rohrbacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

HR 3717 – On December 12, 2013, Representative Tim Murphy (R-PA) introduced the Helping Families in Mental Health Crisis Act of 2013, to make available needed psychiatric, psychological, and supportive services for individuals diagnosed with mental illness and families in mental health crisis, and for other purposes. The bill was referred to the House Committees on: Energy and Commerce; Judiciary; Energy and the Workforce; Ways and Means; and Science, Space and Technology.

S 237 – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S 264 – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

S 265 – On February 7, 2013 Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

S. 348 – On February 14, 2014, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

S. 621 – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

S. 644 – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

S. 1277 – On July 10, 2013, Senator Barbara Boxer (D-CA) introduced the Combating Prescription Drug Abuse Act, to establish a commission for the purpose of coordinating efforts to reduce prescription drug abuse, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

INTERNATIONAL ACTIVITIES

BINATIONAL AGREEMENTS

NIDA–Inserm Create Postdoctoral Drug Abuse Research Fellowships for U.S. and French Scientists

As part of a binational agreement to cooperate on biomedical and health research, the NIDA International Program and Institut National de la Santé et de la Recherche Médicale (Inserm) have created binational postdoctoral research exchange fellowships. In fiscal year 2014, NIDA will support up to two awards for French scientists to work in the United States with a current NIDA grantee, and Inserm will support up to two awards for U.S. scientists to work in France at research units or centers identified by the Inserm Thematic Institute on Neurosciences, Cognitive Sciences, Neurology and Psychiatry. Details about the fellowships, eligibility, and the application process, are online at http://www.drugabuse.gov/international/nida-inserm-postdoctoral-drug-abuse-research-fellowships-us-french-scientists.

RESEARCH RESULTS

Fogarty Review Documents Productivity of NIDA-Supported Tobacco Research

A Fogarty International Center (FIC) review of the NIDA- and FIC-supported International Tobacco and Health Research and Capacity Building Program (TOBAC) has documented outcomes for 34 R01 5-year grants. NIDA contributed $5.3 million for 14 grants awarded between 2002 and 2012. The FIC review cited exceptional outcomes from four NIDA-supported research teams that have published 196 scientific articles and contributed to significant policy and training initiatives in:

- Argentina – A grant to Eliseo Perez-Stable, M.D., University of California San Francisco, and colleagues identified and filled gaps in physician training for smoking cessation programs.
- Brazil – Isabel C. Scarinci, Ph.D., M.P.H., University of Alabama Birmingham, and colleagues used a NIDA grant to leverage support from new Brazilian tobacco control laws in creating an innovative research-training program.
- China – Teh-Wei Hu, Ph.D., University of California Berkley, and colleagues demonstrated the effectiveness of tobacco sales, tax, and crop replacement policies; expanded training opportunities through partnerships among universities, nongovernmental organizations, and foundations; and launched an education campaign that cut smoking rates among pregnant women and their spouses.
- Syria – Three grants to Wasim Maziak, M.D., Ph.D., Florida International University, and colleagues collected the first national prevalence data on water pipe smoking and demonstrated resulting harms, leading the country to ban public smoking and restrict the use of water pipes. A study published in 2011 by researchers at the University of Damascus and the University of Michigan named the Syrian Center for Tobacco Studies as the leading institution for high-quality biomedical research in the nation.

NIDA also supported projects that improved tobacco research and training in Africa, Dominican Republic, Egypt, India, Indonesia, South Africa, and Uruguay. Other FIC partners in the TOBAC program included the National Cancer Institute and the National Institutes of Health Office of the Director. The 34 grants trained more than 3,500 researchers and health care professionals in 30 nations, published 416 scientific articles, and developed 33 curricula. NIDA Director Nora D. Volkow, M.D., and Deputy Director Wilson M. Compton, M.D., M.P.E., participated in the review.

POATS Study Concludes Buprenorphine-Naloxone Outcomes Do Not Depend on Type of Prescription Opioid Abused

Former INVEST/CTN Fellow Suzanne Nielsen, Ph.D., University of Sydney, Australia, is the lead author on an article reporting that dependence on longer-acting opioids was not associated with difficulty in beginning buprenorphine-naloxone treatment. The authors also found that severity of withdrawal affected treatment outcome. The article (The relationship between primary prescription opioid and buprenorphine–naloxone induction outcomes in a prescription opioid dependent sample) reports on the Prescription Opioid Addiction Treatment Study (POATS) and was published early online by *The American Journal on Addictions* (doi: 10.1111/j.1521-0391.2013.12105.x).

MEETINGS

NIDA Director and Other Thought Leaders Meet With His Holiness the Dalai Lama

On October 30, NIDA Director Nora D. Volkow, M.D., participated in *Mind and Life XXVII: Craving, Desire, and Addiction*, a conference of the Mind and Life Dialogues between His Holiness the Dalai Lama and other leading scientists and philosophers. The meeting, which took place at His Holiness the Dalai Lama's private residence in Dharamasala, India, brought together contemplative practitioners, Buddhist and Christian scholars, and leading scientific researchers to achieve new understandings that may ultimately lead to improved treatment of the root causes of craving, desire, and addiction. Since 1987, the Mind & Life Institute has organized annual dialogues between His Holiness the Dalai Lama and leading scientists and philosophers to incorporate two great investigative traditions: modern science and Buddhist philosophy. An audience of about 200 included His Holiness the Dalai Lama, Tibetan monastics, scientists, scholars, contemplatives, and Mind & Life Institute staff and special guests. Dr. Volkow gave an overview titled "The Role of Dopamine in the Addicted Human Brain," which described addiction as a disease and detailed the latest in neuroscience. The complete dialogue between Dr. Volkow and His Holiness the Dalai Lama can be found at http://dalailama.com/webcasts/post/300-mind-and-life-xxvii---craving-desire-and-addiction/4588.

ICADTS Conference Session Explores Role of New Psychoactive Drugs

The 2013 International Council on Alcohol, Drugs and Traffic Safety (ICADTS) conference featured a session on the impact of new psychoactive drugs on traffic safety. IP Director Steven W. Gust, Ph.D., and Marilyn A. Huestis, Ph.D., IRP, co-chaired the session and described the rapid emergence of these designer drugs. By mid-2013, more than 90 nations had reported that

new psychoactive substances were available in their countries, with the 351 new drugs far exceeding the 234 substances controlled under international treaties. Other speakers addressed:

- Driver intoxication attributed to the use of synthetic cannabinoids
- Trends in new psychoactive substances identified by the European Monitoring Centre on Drugs and Drug Addiction
- Efforts to develop urinalysis methods to identify synthetic cannabinoids in humans.

The ICADTS conference was held August 25–29, 2013, in Brisbane, Australia. The conference proceedings are available http://t2013.com/.

NIDA Staff Host U.K. Research Officials

NIDA senior staff and officials from the United Kingdom met August 1, 2013, to discuss animal research regulations, ways to enhance the contribution the life sciences can make to economic growth on both sides of the Atlantic, toxicity testing for emerging synthetic drugs, and areas where U.S. and U.K. drug abuse researchers may be able to collaborate. The United Kingdom is implementing animal research regulations designed to replace animal use, reduce the number of animals used, and refine research procedures to minimize animal suffering. DBNBR Acting Director Joni Rutter, Ph.D., discussed some of the alternative approaches that NIDA is also supporting, while emphasizing the continued need for animal experimentation. NIDA Associate Director for Scientific Affairs Susan Weiss, Ph.D., and IP Director Steven W. Gust, Ph.D., also participated in the meeting. Lord Taylor of Holbeach, U.K. Parliamentary Under Secretary of State for Criminal Information at the Home Office, who is responsible for U.K. regulations on use of animals in research, led the British delegation. Other members of the U.K. delegation included Judy MacArthur Clark, CBE, MRCVS, who heads the Animals in Science Regulation Unit at the Home Office; Dr. Iain Williams from the U.K. Embassy in Washington, DC; and Benedict Collins, Lord Taylor's private secretary.

FELLOWSHIPS

New Humphrey Fellows Meet Federal Officials

Since the start of the fall term at Virginia Commonwealth University (VCU), the 2013 NIDA Hubert H. Humphrey Drug Abuse Research Fellows have met with officials from NIDA, the Substance Abuse and Mental Health Services Administration (SAMHSA), National Institutes of Health (NIH), National Library of Medicine (NLM), and U.S. Department of State.

On September 24, 2013, IP Associate Director Dale Weiss, NIDA International Fellowships Administrator Lisa Jordre, and SAMHSA International Officer Winnie Mitchell introduced NIDA and SAMHSA to the fellows, describing the two agencies' missions, international priorities, and tools to promote collaboration on drug abuse and addiction issues. The three met with each fellow individually to learn about the fellows' goals and to suggest potential professional affiliations.

The NIDA Hubert H. Humphrey Fellows also participated in the U.S. Department of State 2013 Global Leadership Forum. The meeting, which was held October 20–24, 2013, in Washington, DC, gathered 180 Hubert H. Humphrey Fellows from 93 countries. Ms. Weiss and Ms. Jordre joined State Department Foreign Affairs Officer Brian Morales at a discussion session on drug

abuse and international demand reduction. Mr. Morales described train-the-trainer prevention and treatment projects supported by sustainable international partnerships. Participants included 25 Hubert H. Humphrey Fellows from 10 host campuses, Alison Breland of VCU, Lauren Stewart of the Institute of International Education, and former NIDA employee and Hubert H. Humphrey Fellow Petra Jacobs, M.D.

During their October 24, 2013 visit to NIH, Hubert H. Humphrey Fellows from VCU and three other host campuses met with NIH Public Liaison Tara Mowery, who discussed NIH research priorities. NLM Public Affairs Specialist Shana Potash led a tour of the NLM historic book section, which includes rare texts on medicine and disease printed between 1455 and the present, and described library resources available to the general public.

On November 14–15, 2013, the NIDA Hubert H. Humphrey Fellows met with officials at NIDA and SAMHSA. Ms. Weiss chaired a discussion introducing the Institute's research programs. NIDA staff participants included: Stephanie Older, J.D., and Geoffrey Laredo, M.P.A., OSPC; Debra Grossman, M.A., DCNBR; Carmen Rosa, M.S., CCTN; and Jacqueline Lloyd, Ph.D., Augusto Diana, Ph.D., Eve Reider, Ph.D., and Belinda Sims, Ph.D., DESPR. Ms. Mitchell chaired discussions about SAMHSA technical assistance resources for substance abuse treatment, prevention, and behavioral health statistics. SAMHSA officials also hosted small group discussions between the fellows and representatives of the Office of Policy Planning and Innovation, Center for Behavioral Health Statistics and Quality, Center for Substance Abuse Treatment, and Center for Substance Abuse Prevention.

The 2013–2014 NIDA Hubert H. Humphrey Fellows are:

- Fernanda DeConto, M.S. (Brazil) A nurse, Ms. DeConto founded and coordinates a dependence treatment center. She also works for the city of Florianopolis and Florianopolis University Hospital, where she serves on the steering committee for the implementation of emergency psychiatric services. Ms. DeConto hopes to learn new strategies to increase access to treatment, especially for women and youth, learn about quality and effectiveness indicators, and develop evidence-based treatment and prevention programs for drug abuse in Brazil.
- Andrew Dodo (Nigeria) Mr. Dodo is an addiction counselor and vice principal of administration in the Kaduna State Ministry of Education. For the past 20 years, he has conducted drug and alcohol abuse awareness and educational programs, including training programs for teachers and social workers. Mr. Dodo wants to increase his knowledge of evidence-based treatments for women and youth and to develop skills in new treatment methods, conducting public health campaigns and grant writing.
- Martine Hennequin (Mauritius) Ms. Hennequin is a clinical psychologist and psychotherapist who manages a nongovernmental organization (NGO) where she coordinates a team of counselors and developed social reintegration programs for criminal offenders. Her goal is to establish prevention and educational programs that empower poor women and youth in order to reduce unemployment and drug use. Ms. Hennequin would like to learn more about substance abuse policy and prevention and educational programs that could be implemented in her country.
- Asha Hettiarachchige (Sri Lanka) Ms. Hettiarachchige was the first female community corrections officer in Sri Lanka and one of six officers who implemented the Sri Lankan

community corrections system, where she is a senior officer. She trains community corrections recruits and officers and conducts awareness and counseling programs for substance abuse offenders. Ms. Hettiarachchige hopes to use her fellowship experience to design and implement more effective drug control policies and establish drug treatment centers in Sri Lanka.

- Shafqat Huma, M.D. (Pakistan) A psychiatrist, Dr. Huma is a registrar in the Substance Abuse Treatment Unit of Services Hospital Lahore. Dr. Huma plans to expand his knowledge of epidemiology, research methods, and managing substance abuse treatment and prevention services. He would like to acquire the skills and knowledge necessary to develop and implement substance abuse treatment and prevention practices in his home country.
- Walid Hassan Ibrahim, M.D. (Egypt) An assistant psychiatry lecturer at Ain Shams University, Dr. Ibrahim also works with NGOs providing health and education services for refugees in Egypt. He will focus primarily on adolescent tobacco and substance use, and he seeks to obtain more experience in drug abuse policy, prevention, and treatment for adolescents. Dr. Ibrahim also wants to learn how to design public education campaigns and how to improve the training and education of substance abuse professionals.
- Nang Pann Ei Kham, M.B.B.S., M.P.H. (Burma [Myanmar]) is a project manager and trainer focusing on HIV/AIDS programs including capacity building of civil society organizations, research, and advocacy. She helped form the National Drug User Network-Myanmar, which advocates for health and social rights of people who use drugs. Dr. Kham seeks to enhance her knowledge of policies to protect the rights of drug users, community-based prevention and treatment programs for amphetamine-type stimulant use, and developing services for women who use drugs.
- Shehab Mahmoud Hassaan, M.B.B.S., M.Sc. (Egypt) Dr. Mahmoud Hassaan is an assistant lecturer in psychiatry at the Assiut University Institute of Psychiatry and Neuroscience, and a registered inspector responsible for evaluating compulsory psychiatric admissions. Dr. Mahmoud Hassaan will focus on enhancing his leadership and communication abilities, improving his knowledge of research methodology and biostatistics, and developing his ability to conduct community-based research on substance abuse and develop treatment and prevention programs for tramadol addiction.
- Enkelejda Ngjelina, M.P.H., J.D. (Albania) A lawyer and substance abuse counselor, Ms. Ngjelina advocates for the human rights of vulnerable populations. She is a member of the steering committee for the Southeast Europe Drug Policy Network, the European Harm Reduction Network, and the International Drug Policy Consortium. Ms. Ngjelina wants to expand her knowledge of drug treatment and prevention programs, addiction research, and drug abuse cases involving the judicial system.

CTN Invest Fellows

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) have jointly offered fellowships to non-U.S. scientists. Each INVEST fellow works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention. In October 2013, Dr. Greta Zanetti, from the University of Pavia, Italy, joined Dr. Robert Schwartz from the Mid-Atlantic Node for her INVEST fellowship to study cognitive behaviors and addiction. She visited NIDA on November 14, 2013.

INTERNATIONAL VISITORS

A group of visitors from Oman came to NIDA on August 14, 2013. The visitors were invited to the United States under the auspices of the U.S. Department of State's International Visitor Leadership Program. Specific objectives for the visit to the U.S. included looking at how organizations and the government raise awareness regarding youth drug use and how they reach out to parents, study media coverage of youth drug abuse and learn about the role of religion in drug prevention. NIDA staff that met with the group included Liz Davis, OSPC, Harold Perl and Augie Diana, DESPR and Dale Weiss, IP.

Eight members of a Malaysian Task Force Committee on the prevention of drugs, alcohol and substance abuse among students of higher learning education in Malaysia visited NIDA on August 15, 2013. The objectives of the visit were to "study intervention programs on drugs and substance abuse, explore best practices on handling drugs and substance abuse and study the relevant statutes, rules and regulations on drugs prevention". NIDA staff members Augie Diana, Harold Perl DESPR, Jack Stein, OSPC, and Dale Weiss, IP, met with the group.

Under the U.S. Department of State's International Visitor Leadership program a group from Central and South America visited NIDA on December 4, 2013. The objectives of the program were to examine U.S. strategies to address the problem of illicit drug use in the U.S., with a primary focus on demand reduction efforts, provide an overview of the U.S. response, both public and private, to illicit drug use, including education strategies and treatment at the national, state and local levels and demonstrate the diversity of drug abuse prevention and education initiatives through partnerships among key stakeholders: parents, community leaders, local and state governments, law enforcement, educators, researchers and treatment professionals. NIDA staff members Harold Perl, Eve Reider, Aria Crump (DESPR), Carmen Rose (CCTN), Joe Frascella and Lisa Onken (DCNBR) and Dale Weiss (IP) met with the visitors.

OTHER INTERNATIONAL ACTIVITIES

On November 15, 2013, Dr. Harold Perl, DESPR, presented "Advancing Prevention Science at the US National Institute on Drug Abuse" presented at 4th International Conference of the European Society for Prevention Research, held in Paris, France.

Dr. Anto Bonci, IRP Director, presented a seminar at the University of Puerto Rico in September 2013.

Dr. Marilyn Huestis, IRP, presented the plenary lecture at the annual The International Association of Forensic Toxicologists (TIAFT) meeting in Madeira, Portugal entitled "Designer drugs: The new face of drug abuse."

Dr. Marilyn Huestis presented two plenary lectures at the South American Regional International Association of Forensic Toxicologists (TIAFT) meeting in Montevideo, Uruguay, on new designer drugs and neuroadaptation and impaired performance after chronic frequent cannabis smoking.

Dr. Marilyn Huestis was invited by the Ministry of Health and Social Affairs of Sweden to chair a session on "Cannabis and Driving" at the International Conference on Cannabis and Health in Stockholm, Sweden. In addition, she gave two invited lectures at the Karolinska Institute and another at the National Board of Forensic Medicine.

Dr. Yihong Yang, IRP, gave an invited keynote lecture to the International Symposium on Frontiers in Functional Brain Imaging Research - Real Time fMRI in Beijing, China and an invited lecture at the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, in Beijing, China in October 2013.

Dr. John Satterlee, DBNBR, represented the Roadmap Epigenomics Program at the International Human Epigenome Consortium (IHEC) meeting on November 10-12, 2013 in Berlin, Germany and presented an overview of progress made to date. Dr. Satterlee also attended meetings of the European Union and German Epigenomics projects on November 13-14 in Berlin.

Dr. Scott Hall, IRP, served on the program committee of the International Behavioral Neuroscience Group (IBANGS).

PROGRAM ACTIVITIES/FOAs

New NIDA RFAs

On January 17, 2014, NIDA, with NIMH, issued an RFA entitled **Tools for Monitoring and Manipulating Modified RNAs in the Nervous System (R43/R44) RFA-DA-15-001, (R41/R42) RFA-DA-15-002.** The purpose of this initiative is to incentivize small businesses to generate tools and products specifically for monitoring and manipulating covalently modified eukaryotic mRNAs and regulatory RNAs. Open date: March 24, 2014. Application due date(s): April 24, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

New NIDA Program Announcements

On August 26, 2013, NIDA issued a PA entitled **Neuroscience Research on Drug Abuse (R03) PA-13-336, (R21) PA-13-337, (R01) PA-13-338.** The goals of this FOA are to understand the neurobiological mechanisms underlying drug abuse and addiction, with special emphasis on changes that occur during chronic drug use, withdrawal and relapse. An understanding of the basic mechanisms underlying drug addiction can help to identify targets for prevention and treatment interventions. Research utilizing basic, translational, or clinical approaches is appropriate. Open date: January 5, 2014. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On September 11, 2013, NIDA issued a PAR entitled **Early Career Award in Chemistry of Drug Abuse and Addiction (ECHEM) (R21/R33) PAR-13-350**. This PAR seeks to facilitate the entry of new-to-NIH investigators into basic chemistry research applied to drug abuse and addiction. Open date: September 16, 2013. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On November 7, 2013, NIDA issued a PA entitled **Development of Opioid and Adjuvant Fixed Combination Dosage Forms for the Treatment of Chronic Pain with Reduced Addiction Potential (R43/R44) PA-13-387, (R41/R42) PA-13-388.** The purpose of this announcement is to fund meritorious applications from small business organizations that aim to develop of opioid and adjuvant drug combinations within a single dosage form for treatment of a pain condition. The drug combination should provide improved analgesia when compared with the same dose (morphine equivalents) of opioid monotherapy. Such dosage forms should minimize opioid exposure while optimizing analgesia, in order to reduce risk of addiction and limit severity of other opiate adverse effects. Open date: March 5, 2014. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On November 22, 2013, NIDA issued a PAR entitled **Identification of Gene Variants for Addiction Related Traits by Next-Gen Sequencing in Model Organisms Selectively Bred for Addiction Traits (UH2/UH3) PAR-14-010**. The goals of this initiative are to: 1) develop strategies and methodologies for the sequencing, mapping and genomic analyzing of established phenotypes of selectively bred animal models with addiction traits, and 2) identify, from new or existing selectively bred animal models, genetic variants with implications for addiction related traits. Open date: December 31, 2013. Application due date(s): January 31, 2014; June 30, 2014; October 31, 2014; June 30, 2015; October 31, 2015; June 30, 2016; by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 5, 2013, NIDA issued a PA entitled **Functional Genetics, Epigenetics, and Non-coding RNAs in Substance Abuse (R21) PA-14-013**, **(R01) PA-14-014.** This Funding Opportunity Announcement encourages basic functional genetic and genomic research in two areas: 1. functional validation to determine which candidate genes/variants/epigenetic/non-coding RNA features have an authentic role in addictive processes, and 2. detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. Open date: January 5, 2014 (R01), January 16, 2014 (R21). Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On December 6, 2013, NIDA issued a PAS entitled **Public Health Impact of the Changing Policy/Legal Environment for Marijuana (R01) PAS-14-020.** This initiative encourages research on the impact of changing marijuana policies and laws on public health outcomes, including marijuana exposure among children, adolescents, and adults; other licit and illicit drug use; education and professional achievement; social development; risky behaviors (e.g., drugged driving); mental health; HIV, etc. Open date: May 5, 2014. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On December 10, 2013, NIDA issued a PA entitled **Discovering Novel Targets: The Molecular Genetics of Drug Addiction and Related Co-Morbidities (R01) PA-14-025.** This FOA encourages applications for research projects that identify and/or validate chromosomal loci and variations in genes that are associated with vulnerability to addiction and that inform the likelihood of responsiveness to treatment. Applications that propose to examine intermediate phenotypes or endophenotypes to assess the molecular genetics of drug addiction, addiction vulnerability and/or their associated co-morbidities and how they are related to drug addiction are especially encouraged. Open date: January 5, 2014. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

New FOAs Issued by the NIH Roadmap

On November 14, 2013, the NIH Common Fund issued a Roadmap Administrative Supplement entitled **Collaborative Activities to Promote Metabolomics Research (Admin Supp) PA-14-003.** This administrative supplement funding opportunity is part of the Common Fund Metabolomics Program created to increase and improve the nation's ability to undertake metabolomics analyses in translational and clinical research. Metabolomics has great potential to advance our understanding of human diseases, but requires specialized expertise in metabolomics study design, technology, and data analysis and interpretation. This FOA supports supplemental funds to current NIH-funded research projects for new interactive collaborations between basic or clinical researchers and metabolomics experts to add biomedical studies requiring a metabolomics approach. In addition to enhancing the parent grant by adding metabolomics analyses, collaborative projects must include activities to increase the expertise of the biomedical research group in key aspects of metabolomics study design, analysis, and data interpretation. Open date: January 15, 2014. Application due date(s): February 14, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 10, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Computational Analyses Exploiting Reference Epigenomic Maps (R01) RFA-RM-14-001**. This FOA, part of the NIH Common Fund program in Epigenomics, seeks applications from investigators proposing computational analyses that will take advantage of the publicly available reference epigenomic maps generated as part of the Roadmap Epigenomics Program. Open date: February 3, 2014. Application due date(s): March 3, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 12, 2013, the NIH Common Fund issued a Roadmap Administrative Supplement entitled **Administrative Supplement to Existing NIH Director's Biomedical Research Workforce Innovation Award: Broadening Experiences in Scientific Training (BEST) (Admin Supp) PA-14-040**. The purpose of this FOA is to notify all Program Directors/Principal Investigators (PDs/PIs) of the Director's Biomedical Research Workforce Innovation Award: Broadening Experiences in Scientific Training (BEST) Program (**RFA-RM-12-022**) that funds are available for administrative supplements to parent awards in order to help meet the goals of the program. The Administrative Supplement awardee will establish and maintain electronic resources to support the BEST Award investigators in the coordination, collection, and dissemination of approaches and activities that broaden and complement traditional research training in biomedical sciences. The awardee will achieve these goals by developing, facilitating, and managing BEST Award program website(s) and/or portal(s), monthly teleconferences, and the annual meeting in collaboration with NIH personnel. Open date: February 24, 2014. Application due date(s): March 24, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Revisions to Add Single Cell Analysis to Active Research Projects (R01) RFA-RM-13-022, (U01) RFA-RM-13-023.** The purpose of this funding opportunity is to stimulate the adoption and validation of novel powerful single cell analysis (SCA) approaches by supporting collaborations of currently funded U01 investigators with developers of the SCA approaches.

The collaborations must be new, possess the potential to substantially further the aims of the U01 project, and provide iterative and informed feedback to the SCA developers for continued refinement. By strengthening the interface between users and developers, the objective is to accelerate the discovery of fundamental new biological insights and translation of new diagnostic and therapeutic methods that analysis at the single cell level will allow. Open date: March 4, 2014. Application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Revisions to Add Single Cell Analysis to Active Research Projects (R21) RFA-RM-13-021.** This Funding Opportunity Announcement (FOA) issued by the National Institutes of Health, solicits early stage, high-risk/high-impact applications to develop next-generation tools that distinguish heterogeneous states among cells in situ. Applications should define the current state of technology as a benchmark against which the new tool(s) will be measured and should propose proof-of-concept testing of the tool(s) in a complex biological tissue or living organism. The new tools should provide substantially increased sensitivity, selectivity, spatiotemporal resolution, scalability of multiple global or functional measures of single cells. A particular emphasis for this FOA is on measures that minimize cell perturbation and permit viability of cells for repeated measures over time. These novel technologies will aid in obtaining a fine-grained, integrative and dynamic view of heterogeneous cellular states/classes and will provide innovative platforms to transform research into the cellular basis of diseases. Open date: March 4, 2014. Application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Validation and Advanced Development of Technologies for the Study of Biological Properties of Single Cells (R33) RFA-RM-13-020.** This Funding Opportunity Announcement (FOA) invites applications that propose to accelerate the development of promising technologies for single cell analysis by taking them through the downstream optimization and validation process and establishing them as robust, well-characterized tools ready to transform our understanding of the biological properties of individual cells and the role those properties have in modulating the states of surrounding cells, tissues, and organs. This FOA solicits projects where proof-of-principle of the proposed technology or methodology has been established and supportive preliminary data are available. A current R21 award is not necessary. Projects should reflect the potential of single cell analysis to have a major impact on our understanding of biomedical processes, fulfill a critical unmet need by offering compelling advantages to end-users, and demonstrate the technology can be applied to multiple types of cells. It is expected that applications will have well-defined goal(s) with intermediate quantitative milestones. Projects proposing to use established technologies where the novelty resides in the biological or clinical question being pursued will be considered non-responsive and will not be reviewed. Open date: March 4, 2014. Application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH National Research Mentoring Network (NRMN) (U54) RFA-RM-13-017.** The purpose of this Funding Opportunity Announcement (FOA) is to encourage organizations with experience in the mentorship of individuals from diverse backgrounds as they pursue careers in biomedical research to submit grant applications for the NIH National Research Mentoring Network (NRMN). The NRMN will be a nationwide consortium to enhance the training and career development of individuals from diverse backgrounds who are pursuing biomedical, behavioral, clinical, and social science research careers (collectively termed biomedical research careers), through enhanced networking and mentorship experiences. Application due date(s): March 2, 2014. AIDS application due date(s): Not Applicable.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Building Infrastructure Leading to Diversity (BUILD) Initiative (U54) RFA-RM-13-016**. The NIH encourages institutions that seek to engage undergraduate students in innovative mentored research training programs to submit applications for cooperative agreement awards through the NIH Building Infrastructure Leading to Diversity (BUILD) initiative, one of three new Common Fund initiatives that together aim to enhance diversity in the biomedical, behavioral, clinical, and social sciences research workforce. Addressing a major leakage point in the research workforce pipeline, BUILD awards are intended to support the design and implementation of innovative programs, strategies and approaches to transform undergraduate research training and mentorship. BUILD awards will also support institutional and faculty development to further strengthen undergraduate research training environments. Application due date(s): March 2, 2014. AIDS application due date(s): Not Applicable.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Coordination and Evaluation Center for Enhancing the Diversity of the NIH-Funded Workforce Program (U54) RFA-RM-13-015.** The purpose of this Funding Opportunity Announcement (FOA) is to encourage institutions with expertise in data coordination and evaluation of research training, career development, and mentoring programs to submit applications for the establishment and operation of the Coordination and Evaluation Center (CEC) for the NIH Enhancing the Diversity of the NIH-Funded Workforce Program. This program will consist of three integrated initiatives: the Building Infrastructure Leading to Diversity (BUILD) initiative, the National Research Mentoring Network (NRMN) and the CEC. Awardees funded through these initiatives will work together as a consortium which will be coordinated by the CEC. The CEC will facilitate the establishment of program-wide goals and agreed upon hallmarks of successful biomedical researchers at multiple career stages. The CEC will develop appropriate instruments and processes to assess the impact of BUILD and NRMN activities on attainment of these hallmarks by program participants. It will coordinate the collection of data from BUILD and NRMN awardees and other sources, assess the data in an ongoing way, provide feedback to the consortium and facilitate an iterative process of program adjustment to maximize the research benefit of BUILD and NRMN activities. Application due date(s): March 2, 2014. AIDS application due date(s): Not Applicable.

New RFAs Issued as Part of CRAN

On January 3, 2014, NIDA, NIAAA and NCI issued an RFA entitled **Using Social Media to Understand and Address Substance Use and Addiction (R01) RFA-CA-14-008, (R21) RFA-CA-14-009.** This Funding Opportunity Announcement (FOA) is part of a trans-NIH initiative known as Collaborative Research on Addiction (CRAN). The goal of this FOA is to inspire and support research projects investigating the role of social media in risk behaviors associated with the use and abuse of alcohol, tobacco, and other drugs (hereafter referred to as "ATOD") and projects using social media to ameliorate such behaviors. Each research project proposed in response to this FOA must be focused on one of the two distinct areas: 1) observational research using social media interactions as surveillance tools to aid in the understanding of the epidemiology, risk factors, attitudes, and behaviors associated with ATOD use and addiction, or 2) intervention research measuring the reach, engagement, and behavioral and health impact of social media-based interventions for the screening, prevention, and treatment, of ATOD use and addiction. Original research preliminary data are not required but all projects are expected to be supported by a strong rationale that is based on integrating to the extent possible the available relevant information from various sources. Open date: February 25, 2014. Application due date(s): March 25, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

New PAs Issued as Part of CRAN

On August 28, 2013, NIAAA and NIDA issued a PA entitled **Mechanisms of Alcohol and Stimulant Co-Addiction (R01) PA-13-339, (R21) PA-13-340**. This FOA encourages applications from institutions/organizations that propose to study the neurobiological and behavioral mechanisms that might explain how alcohol and stimulants interact at genetic, epigenetic, cellular, neurocircuitry and behavioral levels to promote co-addiction. Open date: January 5, 2014 (R01) January 16, 2014 (R21). Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply.

On December 11, 2013, NIDA with NIAAA, issued a PA entitled **Basic Mechanisms of Brain Development for Substance Use and Dependence (R01) PA-14-026.** This Funding Opportunity Announcement (FOA) encourages Research Project Grant (R01) applications from institutions/organizations that propose to study the developing brain or brain areas that play significant roles in mediating emotional and motivated behavior and in substance use and dependence. All stages of brain development are of interest, but a new emphasis of the current reissue of this initiative is to support basic neuroscience research on fundamental mechanisms of brain development during prepuberty and the adolescent period in relation to the problems of substance abuse and co-morbidity with psychiatric disorders. Topics of interest pertaining to brain development of this initiative include, but are not limited to, the euphoric properties of abused substances, actions of psychotherapeutic agents, and their consequences on memory, cognitive and emotional processes. An additional major goal of this initiative is to understand how exposure to substances of abuse affects the cellular and molecular mechanisms underlying nervous system development and neural circuit functions implicated in substance use and addiction. Open date: January 5, 2014. Application due date(s): Standard dates apply, by 5:00

PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On December 12, 2013, NIDA, with NIAAA, issued a PA entitled **Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R21) PA-14-036, (R03) PA-14-037, (R01) PA-14-038.** The purpose of this Funding Opportunity Announcement (FOA) is to advance research on male-females differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model studies are sought. Open date: January 16, 2014. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On January 7, 2014, NIDA, with NIAAA issued a PA entitled **Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R01) PA-14-061, (R21) PA-14-062, (R03) PA-14-063.** This Funding Opportunity Announcement (FOA) is intended to stimulate model-driven research to understand the ways that people make decisions about engaging in behaviors that impact the risk of acquiring or transmitting HIV, or to adhere to treatments for HIV. Decision making processes may contribute to both substance use/abuse and other HIV acquisition or transmission risks. A better understanding of decision making processes in the context of brain neural networks and their associated functions would lead to the development of better strategies to reduce the frequency of HIV-risk behaviors. Therefore, this FOA encourages applications to study 1) cognitive, motivational or emotional mechanisms and/or 2) brain neuroendocrine and reinforcement systems that related to HIV-risk behaviors or treatment non-compliance. Open date: April 7, 2014. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. The first application due date for this FOA is June 5, 2014. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization. The first AIDS application due date for this FOA is May 7, 2014.

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

Interpreting Variation in Human Non-Coding Genomic Regions Using Computational Approaches and Experimental Assessment (R01) RFA-HG-13-013

Low-Cost, Pragmatic, Patient-Centered Randomized Controlled Intervention Trials (UH2/UH3) RFA-HL-14-019

Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) for Neuroscience and Disorders of the Nervous System (R01) RFA-MH-14-214

BD2K-LINCS-Perturbation Data Coordination and Integration Center (DCIC) (U54) RFA-HG-14-001

Development of an NIH Data Discovery Index Coordination Consortium (U24) RFA-HL-14-031

Mentored Career Development Award in Biomedical Big Data Science for Clinicians and Doctorally Prepared Scientists (K01) RFA-HG-14-007

Open Educational Resources for Biomedical Big Data (R25) RFA-HG-14-009

Courses for Skills Development in Biomedical Big Data Science (R25) RFA-HG-14-008

New PAs Issued by Other NIH/HHS Components in which NIDA is a participant

NIH Support for Conferences and Scientific Meetings (Parent R13/U13) PA-13-347

Academic Research Enhancement Award (Parent R15) PA-13-313

Opportunities for Collaborative Research at the NIH Clinical Center (U01) PAR-13-358

Pre-application: Opportunities for Collaborative Research at the NIH Clinical Center (X02) PAR-13-357

Development of Assays for High-Throughput Screening for Use in Probe and Pre-therapeutic Discovery (R01) PAR-13-364

Research on the Health Determinants and Consequences of Violence and its Prevention, Particularly Firearm Violence (R21) PA-13-369, (R03) PA-13-368, and (R01) PA-13-363

Analysis of Genome-Wide Gene-Environment (G x E) Interactions (R21) PAR-13-382

Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant (Parent T32) PA-14-015

NIH/PEPFAR Collaboration for Implementation Science (Admin Supp) PA-14-024

Administrative Supplements for Research on Sex/Gender Differences (Admin Supp) PA-14-027

Centers for AIDS Research and Developmental Centers for AIDS Research (P30) PAR-14-041

Mentored Patient-Oriented Research Career Development Award (Parent K23) PA-14-049

Mentored Quantitative Research Development Award (Parent K25) PA-14-048

Midcareer Investigator Award in Patient-Oriented Research (Parent K24) PA-14-047

Mentored Clinical Scientist Research Career Development Award (Parent K08) PA-14-046

Independent Scientist Award (Parent K02) PA-14-045

Mentored Research Scientist Development Award (Parent K01) PA-14-044

NIH Pathway to Independence Award (Parent K99/R00) PA-14-042

PHS 2014-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) PA-14-071

PHS 2014-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42] PA-14-072

New RFAs Issued by the NIH Blueprint for Neuroscience Research

BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01) RFA-NS-14-009

BRAIN Initiative: Optimization of Transformative Technologies for Large Scale Recording and Modulation in the Nervous System (U01) RFA-NS-14-008

BRAIN Initiative: New Technologies and Novel Approaches for Large-Scale Recording and Modulation in the Nervous System (U01) RFA-NS-14-007

BRAIN Initiative: Planning for Next Generation Human Brain Imaging (R24) RFA-MH-14-217

BRAIN Initiative: Development and Validation of Novel Tools to Analyze Cell-Specific and Circuit Specific Processes in the Brain (U01) RFA-MH-14-216

BRAIN Initiative: Transformative Approaches for Cell-Type Classification in the Brain (U01) RFA-MH-14-215

Other Program Activities

In September 2013, Dr. Mary Kautz, DCNBR, was nominated to serve as an Alternate Member (along with Member, Dr. Wilson Compton, Acting Deputy Director, NIDA) of the Physical Activity Common Fund Working Group, formed to develop initiatives that will help to determine mechanisms underlying the benefits of physical activity to improve health.

In August 2013, the IRP's Office of Education and Career Development (OECD) concluded a highly successful summer internship program with 53 students from the NIH Summer Internship Program, the NIH Community College Summer Enrichment Program, and the IRP Training Program for Under-represented Populations. Activities included Science Skills Boot Camp; seminars by IRP scientists on their research and the major neurotransmitter systems; workshops on creating and presenting a poster; giving a scientific talk, and applying to graduate and medical school; and two Poster Days, one at the IRP and one at NIH. In conjunction with the DA IRP OECD, IRP hosted two science/math teachers as part of the Baltimore Excellence in STEM

Teaching (BEST) Project. Melissa Angerson teaches science at Severna Park Middle School in Anne Arundel County and worked with Drs. George Uhl and Jana Drgonova on the role of cell adhesion molecules in drug addiction vulnerability. Kathleen Robens teaches statistics at Montgomery Blair High School in Montgomery County and worked with Drs. Steve Heishman and Bill Kowalczyk on the cognitive effects of nicotine in people dually diagnosed with schizophrenia and drug dependence.

CTN Update

A total of 54 CTN protocols have been initiated since 2001, including multi-site clinical trials (38), multi-site surveys (3), studies in special populations (8), and secondary analyses of data across various trials (5). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Over 16,000 participants have been enrolled in CTN studies.
Information on protocols can be found at:
http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies

NIDA's Blending Initiative

Accelerating the dissemination of research-based drug abuse treatment into clinical practice is a priority for the National Institute on Drug Abuse (NIDA) and represents the core mission of the Blending Initiative (http://www.drugabuse.gov/blending-initiative). Through the Blending Initiative, NIDA partners with professional organizations and other institutions dedicated to the training and education of junior fellows/residents to support the development of expertise in substance use disorders (SUDs) within medical and clinical settings. These training awards aim: 1) to promote knowledge of research-based SUD treatment within medical specialties, 2) to advance medical care for patients with substance use disorders, and 3) to facilitate the academic growth, advanced education, and development of future researchers in SUDs and medicine and thereby invest in the future of the field.

Emergency Medicine Foundation (EMF) Awardees:

1) Lauren Whiteside, MD - *Validation of a Risk Prediction Screening Tool for Prescription Opioid Misuse Using Health Information Technology in an ED Sample*

2) Monica Wattana, MD - *Pilot Validation of an Opioid Misuse Risk Measure for Emergency Department Patients with Cancer*

3) Francesca Beaudoin, MD - *Validation of Assessment of Prescription Opioid Use and Misuse Tool in Older Emergency Department Patients*

American Academy of Child and Adolescent Psychiatry (AACAP) Round II Awardees:

1) Lewei (Allison) Lin, MD - *Screening for Prescription Drug Abuse among Adolescents in Primary Care*

2) Amanda Roten, MD - *Cognitive Performance in an Adolescent Marijuana Cessation Pharmacotherapy Trial*

NIDA Special Population Office Update

The NIDA Special Populations Office has a new name: Office of Diversity and Health Disparities. This new name is in-line with the mission of the office which is to 1) increase the number of racial/ethnic under-represented minorities in drug abuse research and 2) ensure that research addressing minority/health disparity populations are adequately represented in NIDA"s extramural research programs.

COMMUNICATIONS

PUBLICATIONS/VIDEOS

NIDA Publications and Online Resources

"Seeking Drug Abuse Treatment: Know What to Ask" (Revised June 2013):
http://www.drugabuse.gov/publications/seeking-drug-abuse-treatment

"Marijuana Facts for Teens" (Revised Oct. 2013):
http://www.drugabuse.gov/publications/marijuana-facts-teens

"Research Report Series: Methamphetamine" (Revised September 2013):
http://www.drugabuse.gov/publications/research-reports/methamphetamine-abuse-addiction

"Heads Up" (Scholastic/NIDA) 2012-13 Teacher's Compilation:
http://www.scholastic.com/smp/pdfs/nida/NIDA_YR11-TE_Comp.pdf

"Heads Up" (Scholastic/NIDA) 2012-13 Student's Compilation:
http://www.scholastic.com/smp/pdfs/nida/NIDA_YR11-Stu_Comp.pdf

NIDA Notes (now online only)

Twenty new articles have been posted on the NIDA Notes homepage. Three new videos (Dave Thomas, Marilyn Huestis, Madeleine Meyer), also available as podcasts, were posted. In addition, the NIDA Notes Homepage was redesigned, improving the search engine, increasing internal referencing and linking, and adding a subscription page for podcasts. NIDA sent out three content e-blasts to 20,000 subscribers and 1 subscription e-blast to NIDA grantees. NIDA Notes had 32,000 page views from mid-October to mid-November.

"Principles of Adolescent Substance Use Disorder Treatment: A Research Based Guide" (Released January 2014)
http://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide

"Substance Use Disorders in Adolescents: Screening and Engagement in Primary Care Settings" (Released January 2014)
http://webcampus.drexelmed.edu/nida/module_2/default_FrameSet.htm

Heads Up: "Drugs and Your Body: It Isn't Pretty" (Scholastic/NIDA) (January 2014)
http://www.scholastic.com/drugs-and-your-body/
A new Web interactive designed for grades 7-12 that uses graphics, videos and quizzes to demonstrate the wide-ranging harmful effects of drugs on the brain and body.

Videos

- **CEWG Region Report: Drug Abuse in Philadelphia, June 2013** http://youtu.be/CiAxo0MFEXo
- **NIDA NOTES: NIDA@Work Presents, Dr. Dave Thomas** http://youtu.be/c-Wixxy5lYA
- **National Drug Facts Week: Do You Have Something to Say? Teens Do.** http://youtu.be/JIihA4FeT2c
- **CEWG Region Report: Drug Abuse in Detroit, Wayne County, and Michigan, June 2013** http://youtu.be/jwRWmgniF6Q
- **What's New at NIDA: Office of Science Policy and Communication Director's notes** http://youtu.be/PyFYgxR-4sk
- **Chat Day, NDFW, release June 2013** http://www.youtube.com/watch?v=1HlsRRjwa2I
- **I-Science Chief Resident Program, June 2013** http://www.youtube.com/watch?v=iBRL_KkwxI8
- **Jane Maxwell, CEWG, Emerging Drug, Lean** http://youtu.be/RJfYbUfDaqI
- **Carol Boyd, CEWG, Prescription Drug Use** http://youtu.be/bORYUoQrfDU
- **Drs. Brooks, NIDATV** http://www.youtube.com/watch?v=U7hOpCiJlSQ
- **What's New at NIDA/Jack Stein, August Insite** http://youtu.be/D_tlCecHEDk
- **I-Science, Evidence Based Practices** http://youtu.be/b3zNDnBoZLY
- **I-Science: NIDA's Look into Old Designer Drugs, New Cultural Phenomenon** http://youtu.be/FZMgIO2tC18
- **I-Science: NIDA's Look into the Risks of Designer Drugs** http://youtu.be/-WWNwW0aDh4
- **NIDA TV Spotlight on the Iraqi Community Epidemiology Work Group (CEWG)** http://youtu.be/3mnM5nxZgIs
- **NIDATV Scientist Spotlight (Cannabinoid), release Aug 2013** http://youtu.be/Zyh-N3k30jg and http://youtu.be/DsE9_aJfZGw
- **Duke University Dr. Meier Interview, Aug 2013** http://youtu.be/qJXnxHYapbE
- **Teen MOTS, August 2013** http://youtu.be/dWfnzQqVMVs
- **Avant-Garde Award 2013** http://youtu.be/J9sZmWwBqbk
- **Dr. Volkow: Addicted Human Brain (For CMI)** http://www.youtube.com/watch?v=1J87LFHlkp8
- **NIDA TV Spotlight: "Recovery: What's Research Got to do with It, Part II"** http://youtu.be/QYxi4HhpXhw
- **NIDA TV Spotlight: "Recovery: What's Research Got to do with It, Part I"** http://youtu.be/2M4rYZU48EM
- **NIDA NOTES: NIDA@Work Presents, Dr. Marilyn Huestis** http://youtu.be/hn2jVa5Izrg
- **2013 ISEF Addiction Science Award Winners Visit NIDA** http://youtu.be/ZjLfwyyEILI
- **I-Science: NIDA's Look into what we still need to know about Synthetic Cannabinoids** http://youtu.be/SP667cI6NA

- **NIDATV Scientist Spotlight (E-cig), Release Oct 2013** http://www.youtube.com/watch?v=Iz67IqkLwYs
- **MTF: Dr Volkow on Marijuana** http://www.youtube.com/watch?v=piN8m2OfimM&feature=c4-overview&list=UUfXHx9qyqeB3ezHQnHk8zXA
- **MTF: Drs. Volkow and Compton** http://www.youtube.com/watch?v=Ki5k4Xetv3I&feature=c4-overview&list=UUfXHx9qyqeB3ezHQnHk8zXA
- **MTF: Dr. Johnston** http://www.youtube.com/watch?v=_4KkEAXUYuM&feature=c4-overview&list=UUfXHx9qyqeB3ezHQnHk8zXA

CTN-Related Publications

Six editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 28 CTN studies are now available on the NIDA Data Sharing website http://www.nida.nih.gov/CTN/Data.html. Over 2,000 data sets have been downloaded by researchers from 45 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

Other Publications

Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, Glasser MF, Curtiss S, Dixit S, Feldt C, Nolan D, Bryant E, Hartley T, Footer O, Bjork JM, Poldrack R, Smith S, Johansen-Berg H, Snyder AZ, Van Essen DC. Function in the human connectome: task-fMRI and individual differences in behavior. WU-Minn HCP Consortium. Neuroimage. 2013 Oct 15; 80: 169-189.

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Bjork JM, Grant SJ, Chen G, Hommer DW. Dietary tyrosine/phenylalanine depletion effects on behavioral and brain signatures of human motivational processing. Neuropsychopharmacology. 2013 Sep 2. doi: 10.1038/npp.2013.232. [Epub ahead of print]

Chatterji S, Alonso J, Petukhova MV, Vilagut G, Glantz MD, Khalaf MS. Disability Associated with Common Mental and Physical Disorders. In J. Alonso, S. Chatterji, and Y. He (Eds.). The Burdens of Mental Disorders: Global Perspectives from the WHO World Mental Health Surveys. New York: Cambridge University Press, pp. 186-194, 2013.

Metsch LR, Feaster DJ, Gooden L, Schackman BR, Matheson T, Das M, Golden MR, Huffaker S, Haynes LF, Tross S, Malotte CK, Douaihy A, Korthuis PT, Duffus WA, Henn S, Bolan R, Philip SS, Castro JG, Castellon PC, McLaughlin G, Mandler RN, Branson B, Colfax GN. Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: the AWARE randomized clinical trial JAMA. 2013 Oct 23; 310(16): 1701-1710.

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Straus MM, Ghitza UE, Tai B. Preventing deaths from rising opioid overdose in the US - the promise of naloxone antidote in community-based naloxone take-home programs. Subst Abuse Rehabil. 2013 Sep 2; 2013(4).

Tai B, Saxon AJ, Ling W. Medication-assisted therapy for opioid addiction. J Food Drug Anal. 2013 Dec; 21(4) Suppl: S13-S15.

Volman SF, Lammel S, Margolis EB, Kim Y, Richard JM, Roitman MF, Lobo MK. New insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. J Neurosci. 2013 Nov 6; 33(45): 17569-17576.

Dr. Dionne Jones, DESPR, Services Research Branch co-authored a book chapter, Future Directions in Culturally Competent Health Care Delivery for Underserved Populations in P. Kinsey and D. Louden (Eds.). *Ethnicity, Health and Well Being*, 2013.

Dr. Jacqueline Lloyd, DESPR, Prevention Research Branch is co-author with Dr. Katrina Baum (Department of Justice), Katherine Blakeslee (Institute of Medicine), and Dr. Anthony Petrosino (WestEd) on an Institute Of Medicine discussion paper titled "Violence Prevention: Moving from Evidence to Implementation." The paper was released and posted to the IOM website on October 18, 2013 alongside the workshop summary for *The Evidence for Violence Prevention Across the Lifespan and Around the World*, which took place January 23-24, 2013.

COMMUNITY AND PRESS EVENTS

2013 winners of Addiction Science Award present at NIDA
The 2013 winners of NIDA's Addiction Science Awards, part of the Intel International Science and Engineering Fair (ISEF), presented their projects to NIDA Director Nora Volkow and other NIDA scientists on August 13, 2013, and were given a tour of the NIH campus. The Addiction Science Awards are coordinated by NIDA as well as Friends of NIDA, a private group dedicated to furthering NIDA's mission. ISEF is the world's largest science competition for high school students.

NIDA participates in Facebook Chat with Partnership at DrugFree.org.
On September 16, 2013, Dr. Volkow participated in a live Facebook chat with the Partnership at Drugfree.org for its "Meet the Parents Hour," which aims to provide science-based information to parents and those affected by drugs and alcohol. Over 3,300 people were reached during the hour-long chat, with close to 40 questions answered.

Dr. Nora Volkow Honored at Child Mind Institute Event
On October 1, 2013, the Child Mind Institute hosted its third annual *On the Shoulders of Giants* scientific symposium, honoring NIDA Director Nora Volkow and two of her scientific mentees. Dr. Volkow's pre-recorded video presentation summed up her groundbreaking work in drug addiction and focused on chemical dependency as a disease of the brain.

NIDA IRP Hosts Mentor Foundation USA "Shatter the Myths" Event
On October 30, 2013, NIDA provided press support to an IRP event with the Mentor Foundation USA in an effort to "Shatter the Myths" about drug abuse. Nearly 200 high school students were in attendance at the Johns Hopkins Bayview Medical Center in Baltimore, MD. The goal of the event was to give teenagers a forum to learn about the dangers of drug abuse, ask questions and get scientific answers about substance abuse. IRP Scientific Director Dr. Antonello Bonci was interviewed by *A&E TV* and *WBAL-11* (a local NBC affiliate) regarding his presentation. NIDA staff live-tweeted from the event. Other speakers included Baltimore City Mayor Stephanie Rawlings-Blake, Office of National Drug Control Policy Deputy Director David Mineta, and Dr. Lonise Bias, mother of the late Len Bias.

NIDA Director and other thought leaders meet with His Holiness the Dalai Lama
On October 30, 2013, Dr. Volkow participated in *Mind and Life XXVII: Craving, Desire, and Addiction*, a conference of the Mind and Life Dialogues between His Holiness the Dalai Lama and other leading scientists and philosophers. The meeting, which took place at His Holiness the Dalai Lama's private residence in Dharamasala, India, brought together contemplative practitioners, Buddhist and Christian scholars, and leading scientific researchers to achieve new understandings that may ultimately lead to improved treatment of the root causes of craving, desire and addiction. An audience of about 200 included His Holiness the Dalai Lama, Tibetan monastics, scientists, scholars, contemplatives, Mind & Life Institute staff, and special guests. Dr. Volkow gave an overview titled *The Role of Dopamine in the Addicted Human Brain*, which described addiction as a disease and detailed the latest in neuroscience. Her presentation and interaction with the Dalai Lama are posted on the NIDA Web site

(http://www.drugabuse.gov/about-nida/noras-blog/2013/11/talking-to-dalai-lama-about-addiction-science)

Dr. Nora Volkow participated in NIH-Sponsored Press Conference at SfN
On November 10, 2013, Dr. Volkow presented the status of NIDA's research at the Society of Neuroscience in San Diego, CA. NIDA posted tweets on its Twitter account surrounding the event.

Press Releases

August 29, 2013
2013 Avant-Garde Awards explore HIV without AIDS, protective genes
NIH's HIV/AIDS research awards will also look at vaccine innovations
With proposals ranging from a combined cocaine/HIV vaccine to unlocking the mystery of genes that protect some people from the ill effects of HIV, three American scientists have been chosen to receive the 2013 Avant-Garde Award for HIV/AIDS Research from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The three scientists, Drs. Warner Greene, Richard Sutton, and Timothy Cardozo, will each receive $500,000 per year for five years to support their research. NIDA's annual Avant-Garde award competition, now in its sixth year, is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug users.

Awardees are:
Awardee: Warner Greene, M.D., Ph.D., Gladstone Institutes, San Francisco
Project: HIV without AIDS: A radically different approach to help the developing world
Dr. Greene's research team is taking a unique approach to treat HIV infection -- rather than attempting to suppress the virus, they are investigating a way to modify how an animal model responds to the virus. By inhibiting the caspase I enzyme and preventing the inflammatory and immune responses that lead to the death of specific immune cells (CD4 T-cells) following HIV infection, their approach could prevent further CD4 T-cell loss that eventually results in clinical progression to AIDS. A single inhibitor could be significantly more cost-effective than combination antiviral therapies, providing a much-needed treatment option for vulnerable populations like injection drug users in the developing world, who likely have limited access to antiviral medications.
"We can potentially help millions who carry HIV if our studies of an existing class of anti-inflammatory drugs are successful," said Greene. "These drugs could provide a lifesaving bridge to treatment for those without access to antiretroviral medications—and for those on antiretrovirals but who are at risk for premature onset of diseases associated with aging. It is also possible that these drugs will attack the latent viral reservoir and thus contribute to a cure for HIV/AIDS."

Awardee: Richard Sutton, M.D., Ph.D., Yale University, New Haven, Conn.
Project: Host genetic control of HIV
Dr. Sutton's research team plans to identify those rare genetic mutations that account for why a small percentage of HIV-infected individuals do not suffer any ill effects or need to take antiretroviral medications. Sutton will integrate a variety of techniques to isolate specific

protective genes, including viral growth assays, the latest genomic technologies, and genetic analyses of family members (for example, siblings, parents, children, aunts, uncles, and cousins) to better understand inheritance patterns for these protective genes and to identify which variants are responsible for control of HIV.

"This award will give our research team at Yale a great opportunity to fully explore how some individuals who are infected with HIV are able to control the virus," said Sutton. "By recruiting several different patient populations, including those who use substances, it is hoped that these studies will benefit all those now living with HIV and also accelerate the vaccine effort."

Awardee: Timothy Cardozo, M.D., Ph.D., New York University Langone Medical Center
Project: Combined cocaine and HIV vaccine

Dr. Cardozo's group plans to test a combined anti-cocaine/HIV vaccine in animal models. The ultimate goal is to produce a clinical-grade vaccine, the prototype of which is sought by the end of the project period. A successful vaccine of this kind would treat cocaine addiction while preventing HIV infection in those receiving the vaccine. Compared to the general population, women and disadvantaged minorities show higher incidence of cocaine use linked to HIV infection. This combined vaccine could be a high-impact intervention for these populations.

"A vaccine that can generate antibodies protecting against the effects of an abused substance like cocaine and also against HIV would be an unprecedented medicine directly targeting the intersection of substance abuse and HIV/AIDS," Cardozo said. "Based on recent findings, we developed a game plan to engineer such a medicine, and, with Avant-Garde support, we now have a historic opportunity to pursue this goal."

"What's especially exciting about this year's award recipients is that these interventions can have a significant impact on reducing HIV infection world-wide," said NIDA Director Nora D. Volkow, M.D. "We expect that this innovative research will provide new leads in the fight against HIV/AIDS – especially for those populations that have been historically hard to reach with current therapies."

These awardees were among the many applicants whose proposals reflect diverse scientific disciplines and approaches to HIV/AIDS research. The Avant-Garde Awards are modeled after the NIH Pioneer Awards and are granted to scientists of exceptional creativity who propose high-impact research that could open new avenues for prevention and treatment of HIV/AIDS among drug abusers.

For information about NIDA's AIDS Research Program, including the Avant-Garde Award Program for HIV/AIDS Research, go to www.drugabuse.gov/AIDS.

Greene, Sutton, and Cardozo are funded under grant numbers DA036502, DA036463 and DA036478, respectively.

http://www.drugabuse.gov/news-events/news-releases/2013/08/2013-avant-garde-awards-explore-hiv-without-aids-protective-genes

September 9, 2013

National Drug Facts Week 2014 begins January 27

NIH-led observance connects teens with drug abuse experts

As the school year begins, the National Institute on Drug Abuse (NIDA) encourages educators, community groups and parents to begin planning events for the fourth annual National Drug Facts Week in the last week of January. Hundreds of educational events are expected around the

country to connect teens with scientific experts in the drug abuse field. The observance coordinated by NIDA, part of the National Institutes of Health, begins Jan. 27 and ends Feb. 2, 2014.

National Drug Facts Week encourages and stimulates community-based events where teens ask questions of addiction scientists or health experts. Events can be sponsored by a variety of organizations, including schools, community groups, sports clubs, and hospitals. Topics for discussion include the science behind illicit drug use, prescription drug abuse, and use of alcohol and tobacco. Event holders who register will receive free booklets with science-based facts about drugs, designed specifically for teens.

The event registration site is http://drugfactsweek.drugabuse.gov

http://www.drugabuse.gov/news-events/news-releases/2013/09/national-drug-facts-week-2014-begins-january-27

October 21, 2013

NIDA's drug abuse information for teens goes mobile

NIH also improves access for parents, teachers, and Spanish language readers

Teens -- and adults who care for them -- can now find answers to questions about drug abuse and addiction more easily, and through smartphones and tablets. Spanish language versions of easy to understand resources on drug abuse and addiction are now also available. The updates, announced today by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, are being launched as part of National Substance Abuse Prevention Month events in October.

For teens, their parents and teachers, NIDA has upgraded its popular teen website to a "responsive design" model that automatically adjusts to fit the viewer's screen for better viewing through smartphones and tablets. The new design is also more engaging, with larger, more vibrant buttons that link directly to resources that provide answers to questions and concerns related to drug abuse in adolescents. The teen site continues to house free, interactive resources such as its teen blog and PEERx, an online educational initiative to discourage abuse of prescription drugs among teens.

In addition to the redesigned teen site, NIDA's improved Parents and Educators page makes it easier for caregivers and teachers to find free, scientifically based prevention and education resources. Examples include Family Checkup -- a tool for talking with children about drugs -- as well as the latest science-based information on the health effects and consequences of drug abuse. Teachers can also find free resources for elementary, middle and high school students, including examples of classroom-based science experiments from the NIH Lab Challenge.

To reach adults with limited literacy skills, NIDA's Easy-to-Read website now includes Spanish-language versions of its Drug Facts pages; its What is Addiction? section; as well as two easy to understand videos explaining the science behind drug addiction.

In October, parents, youth, schools, businesses and community leaders across the country join together in recognizing the role that substance abuse prevention plays in promoting safe and healthy communities. National Substance Abuse Prevention Month, which began in 2011, is organized by the White House's Office of National Drug Control Policy (ONDCP).

"By using improved Web and handheld device strategies to distribute research findings, we can reach a broader audience," said NIDA Director Dr. Nora D. Volkow. "NIDA is launching these

tools during National Substance Abuse Prevention Month and will continue to translate the science to guide effective prevention and education efforts in homes and communities."
For more information on drug prevention, see NIDA's Preventing Drug Abuse among Children and Adolescents at www.drugabuse.gov/publications/preventing-drug-abuse-among-children-adolescents. To find out how to get involved in National Substance Abuse Prevention Month, visit www.whitehouse.gov/ondcp/prevention-intro/prevention-month.
http://www.drugabuse.gov/news-events/news-releases/2013/10/nidas-drug-abuse-information-teens-goes-mobile

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November 8, 2013

Dr. Wilson Compton named Deputy Director, National Institute on Drug Abuse

Wilson Compton, M.D., M.P.E., a nationally known expert on the causes and prevention of drug abuse, has been appointed the Deputy Director of the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The announcement was made today by the Institute Director, Dr. Nora Volkow.

Dr. Compton has served as the Director of NIDA's Division of Epidemiology, Services and Prevention Research since 2002. As Division Director, he has managed a complex research program of national and international scope addressing the extent and causes of drug abuse and the development of effective prevention strategies. He has also coordinated innovative research designed to strengthen addiction treatment services through improved organizational and financial infrastructure. In addition, Dr. Compton has been a member of the DSM-5 Task Force and the Substance Use Disorders Workgroup for the past five years.

"I look forward to working with Dr. Compton as NIDA responds to growing challenges in the substance abuse research field," said NIDA Director Dr. Nora D. Volkow. "In more than a decade as a Division Director here at NIDA, he has built a formidable team supporting research into the extent and causes of substance abuse, with a strong focus on tobacco, prescription and illicit drug abuse. His passion is unwavering, and his enthusiasm to use science to find improved approaches to substance abuse management will inspire us all."

Recently, Dr. Compton has been leading an effort jointly sponsored by NIDA and the Food and Drug Administration's Center for Tobacco Products to field a large scale longitudinal population study to assess the impact of new tobacco regulations. This landmark study is expected to include over 50,000 persons in the U.S. ages 12 and older with yearly data collection from study participants, including both surveys and biological assessments of tobacco exposures, risk factors and health outcomes. He will continue to be involved in this effort in his new role.

"I am so excited to be working with Dr. Volkow and the entire NIDA team to use drug abuse science to improve health. Applying the newest scientific techniques to understanding and solving problems related to drug abuse is challenging, fascinating and essential," said Compton. "NIDA is a wonderful place to work, and our scientific mission is critical as we face multiple issues in our communities related to addictions. I am really pleased to help Dr. Volkow surmount these challenges in leading this dynamic and fantastic organization."

In October 2013, Dr. Compton was one of ten people to receive the Health and Human Services Secretary's Award for Meritorious Service, which recognizes employees for their sustained excellence and for inspiring others to improve their performance. Dr. Compton was recognized for outstanding cross-agency collaborations, linking NIDA with multiple Health and Human

Services and outside agencies to reduce tobacco use and prescription drug abuse, and to improve substance abuse prevention and treatment systems.
Prior to joining NIDA, Dr. Compton was Associate Professor of Psychiatry and Director of the Master in Psychiatric Epidemiology Program at Washington University in Saint Louis as well as Medical Director of Addiction Services at the Barnes-Jewish Hospital in Saint Louis. Dr. Compton received his undergraduate education from Amherst College. He attended medical school and completed his residency training in psychiatry at Washington University.
http://www.drugabuse.gov/news-events/news-releases/2013/11/dr-wilson-compton-named-deputy-director-national-institute-drug-abuse

December 10, 2013
Stimulant-addicted patients can quit smoking without hindering treatment
New NIH study dispels concerns about addressing tobacco addiction among substance abuse patients
Smokers who are addicted to cocaine or methamphetamine can quit smoking while being treated for their stimulant addiction, without interfering with stimulant addiction treatment. This is according to new research funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.
According to the Substance Abuse and Mental Health Services Administration, in 2008, 63 percent of people who had a substance use disorder in the past year also reported current tobacco use, compared to 28 percent of the general population. In fact, smoking tobacco causes more deaths among patients in substance abuse treatment than the substance that brought them to treatment. Despite this, most substance abuse treatment programs do not address smoking cessation.
"Substance abuse treatment programs have historically been hesitant to incorporate concurrent smoking cessation therapies with standard drug addiction treatment because of the concern that patients would drop out of treatment entirely," said NIDA Director Dr. Nora D. Volkow. "However, treating their tobacco addiction may not only reduce the negative health consequences associated with smoking, but could also potentially improve substance use disorder treatment outcomes."
In this study, published today in the Journal of Clinical Psychiatry, some cocaine and/or methamphetamine-dependent patients in substance abuse treatment were randomly assigned to also receive smoking cessation treatment. Treatment included weekly counseling sessions and extended-release bupropion during weeks one through 10; and a nicotine inhaler and contingency management, which awards prizes to encourage smoking cessation, during weeks four through 10. Outcomes were measured by drug and carbon monoxide testing, and by self-report during the 10-week trial and at a three- and six-month follow-up. Results showed that smoking cessation therapy significantly increased smoking quit rates – both during treatment and at follow-up – without negatively affecting participation in stimulant addiction treatment.
“These findings, coupled with past research, should reassure clinicians that providing smoking-cessation treatment in conjunction with treatment for other substance use disorders will be beneficial to their patients,” said Dr. Theresa Winhusen, from the University of Cincinnati College of Medicine and first author on the study.
For a copy of the article by Winhusen et al., go to www.psychiatrist.com/privatepdf/article_wrapper.asp?art=oap/13m08449/13m08449.htm. For a

related article by the first author, exploring the role of mentholated cigarettes in cocaine and methamphetamine dependence, go to: www.drugandalcoholdependence.com/article/S0376-8716%2813%2900362-1/abstract. For more information on nicotine and cocaine, go to www.drugabuse.gov/drugpages/nicotine.html and www.drugabuse.gov/drugpages/cocaine.html.

This study was funded by NIH, NIDA under grants DA013045, DA013720, DA013727, DA013732, DA015815, DA020024, and DA020036. The ClinicalTrials.gov identifier is NCT01077024.

http://www.drugabuse.gov/news-events/news-releases/2013/12/stimulant-addicted-patients-can-quit-smoking-without-hindering-treatment

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December 18, 2013

Sixty percent of 12th graders do not view regular marijuana use as harmful

NIH's 2013 Monitoring the Future Survey shows high rates of marijuana use; decreases in abuse of pain relievers and synthetic drugs

The percentage of high-schoolers who see great risk from being regular marijuana users has dropped dramatically in the past 10 years, according to this year's Monitoring the Future (MTF) survey, which measures drug use and attitudes among the nation's eighth-, 10th-, and 12th-graders. The change in attitudes is reflected in continued high rates of marijuana use in all three grades and could predict higher use in future years, based upon past MTF data showing an association between softening attitudes and increased use of marijuana.

The survey reports that 39.5 percent of 12th graders view regular marijuana use as harmful, down from last year's rate of 44.1 percent, and considerably lower than rates from the last two decades.

The rates of marijuana use have also shown significant changes in the past two decades, with 6.5 percent of seniors smoking marijuana daily compared to 6 percent in 2003 and 2.4 percent in 1993.

"This is not just an issue of increased daily use," said NIDA Director Nora D. Volkow, M.D. "It is important to remember that over the past two decades, levels of THC – the main psychoactive ingredient in marijuana – have gone up a great deal, from 3.75 percent in 1995 to an average of 15 percent in today's marijuana cigarettes. Daily use today can have stronger effects on a developing teen brain than it did 10 or 20 years ago."

Nearly 23 percent of seniors say they smoked marijuana in the month prior to the survey, and just over 36 percent say they smoked it during the past year. For 10th graders, 4 percent say they use marijuana daily, with 18 percent reporting past month use and 29.8 percent reporting use in the previous year. More than 12 percent of eighth graders say they used marijuana in the past year.

"We should be extremely concerned that 12 percent of 13- to 14-year-olds are using marijuana," Volkow added. "The children whose experimentation leads to regular use are setting themselves up for declines in IQ and diminished ability for success in life."

"These increases in marijuana use over the past few years are a serious setback in our nation's efforts to raise a healthy generation of young people," said Gil Kerlikowske, director of National Drug Control Policy. "Teens deserve to grow up in an environment where they are prepared to meet the challenges of the 21st century, and drug use never factors into that equation. Today's news demands that all of us recommit to bolstering the vital role prevention and involved parenting play in keeping young people safe, strong, and ready to succeed."

There is mixed news regarding abuse of prescription medications. The survey shows continued abuse of Adderall, commonly used to treat attention deficit hyperactivity disorder, or ADHD, with 7.4 percent of seniors reporting taking it for non-medical reasons in the past year. However, only 2.3 percent of seniors report abuse of Ritalin, another ADHD medication. Abuse of the pain reliever Vicodin has shown a marked decrease in the last 10 years, now measured at 5.3 percent for high school seniors, compared to 10.5 percent in 2003. In addition, 5 percent of seniors report abuse of cough products containing dextromethorphan, down from 6.9 percent in 2006, the first year it was measured by the survey.

There are some other bright spots in this year's survey. Past year use of K2 or Spice, sometimes called synthetic marijuana, dropped to 7.9 percent among high school seniors from 11.3 percent last year. While many of the ingredients in synthetic cannabinoids have been banned by the U.S. Drug Enforcement Administration, Spice manufacturers have attempted to substitute other chemicals in their mixtures, and many young people continue to experience toxic reactions to these substances.

The use of substances commonly known as bath salts is at or under 1 percent in all three grades. Bath salts refers to an emerging family of drugs containing one or more synthetic chemicals related to cathinone, an amphetamine-like stimulant found naturally in the khat plant. Use of the hallucinogenic herb salvia is declining, with 3.4 percent of 12th-graders reporting past year use, compared to 5.9 percent in 2011 and 4.4 percent last year.

The past year use of inhalants in all three grades has declined. Among eighth-graders, the 2013 rate is at 5.2 percent, compared to 8.7 percent 10 years ago and 11.0 percent 20 years ago. Inhalants are among the abused substances that have higher rates of use by the younger students in the survey. Four percent of seniors report use of Ecstasy (MDMA) in the previous year, still considerably lower than 2001, when use peaked at 9.2 percent.

For cocaine and heroin, while there was no significant change from the 2012 rates, there continues to be a gradual decline in use, with both drugs at historic lows in all three grades. The 2013 rate for high school seniors for past year cocaine use is 2.6 percent, compared to a peak of 6.2 percent in 1999. Similarly, the reported use of heroin by 12th-graders is 0.6 percent this year, compared to a peak of 1.5 percent in 2000.

Cigarette smoking continues to decline as well. For the first time, the percentage of students in all three grades combined who say they smoked in the past month is below 10 percent (9.6 percent) compared to 16.7 percent 10 years ago and 24.7 percent in 1993. Daily smoking of cigarettes is now at 8.5 percent for 12th-graders, 4.4 percent for 10th-graders, and 1.8 percent for eighth-graders. However, 21.4 percent of seniors report smoking tobacco with a hookah in the past year, more than 3 percent above the rate teens reported in 2012 (18.3 percent).

"While cigarette use among youth continues to decline, such progress is threatened by use of other tobacco products such as hookahs," said Howard K. Koh, M.D., M.P.H., assistant secretary for health for the U.S. Department of Health and Human Services. "We must remain vigilant in protecting kids against both old and new agents that promote addiction."

The use of alcohol by teens continues its steady decline. For 12th-graders, alcohol use peaked in 1997, with more than half (52.7 percent) reporting drinking alcohol in the past month. Only 39.2 percent of seniors reported past month use this year. An indicator of binge drinking (defined in the survey as five or more drinks in a row at least once in the past two weeks) stayed the same as last year for eighth-graders (5.1 percent) but dropped considerably for 10th-graders (to 13.7 percent from 15.6 percent in 2012.) The 2013 binge drinking rate for 12th-graders is 22.1 percent.

In 2012, the survey added questions about where students get marijuana. Looking at the last two years combined, 34 percent of marijuana-using 12th-graders living in states with medical marijuana laws say that one of the ways they obtain the drug is through someone else's medical marijuana prescription. In addition, more than 6 percent say they get it with their own prescription. The team of investigators who conduct the survey will continue to explore the link between state laws and marijuana's accessibility to teens.

Overall, 41,675 students from 389 public and private schools participated in this year's Monitoring the Future survey. Since 1975, the survey has measured drug, alcohol, and cigarette use and related attitudes in 12th–graders nationwide. Eighth- and 10th-graders were added to the survey in 1991. Survey participants generally report their drug use behaviors across three time periods: lifetime, past year, and past month. Questions are also asked about daily cigarette and marijuana use. NIDA has provided funding for the survey since its inception by a team of investigators at the University of Michigan at Ann Arbor, led by Dr. Lloyd Johnston. MTF is funded under grant number DA001411. Additional information on the MTF Survey, as well as comments from Dr. Volkow, can be found at www.drugabuse.gov/drugpages/MTF.html.

MTF is one of three major surveys sponsored by the U.S Department of Health and Human Services that provide data on substance use among youth. The others are the National Survey on Drug Use and Health and the Youth Risk Behavior Survey. The MTF website is: www.monitoringthefuture.org. Follow Monitoring the Future 2013 news on Twitter at @NIDANews, or join the conversation by using: #MTF2013. Additional survey results can be found at www.hhs.gov/news or www.whitehouse.gov/ondcp. Information on all of the surveyed drugs can be found on NIDA's Web site: www.drugabuse.gov.

The National Survey on Drug Use and Health, sponsored by the Substance Abuse and Mental Health Services Administration, is the primary source of statistical information on substance use in the U.S. population 12 years of age and older. More information is available at: http://www.samhsa.gov/data/NSDUH.aspx.

The Youth Risk Behavior Survey, part of HHS' Centers for Disease Control and Prevention's Youth Risk Behavior Surveillance System, is a school–based survey that collects data from students in grades nine–12. The survey includes questions on a wide variety of health–related risk behaviors, including substance abuse. More information is available at www.cdc.gov/HealthyYouth/yrbs/index.htm.

http://www.drugabuse.gov/news-events/news-releases/2013/12/sixty-percent-12th-graders-do-not-view-regular-marijuana-use-harmful

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NIDA Hosts Monitoring the Future Survey Teleconference; Reaches Millions via Media Coverage

On December 18, NIDA hosted its first teleconference announcing the 2013 Monitoring the Future Survey results. Featured speakers included NIDA Director Dr. Nora Volkow, ONDCP Director R. Gil Kerlikowske and Principal Investigator Dr. Lloyd Johnson from the University of Michigan. Approximately 25 reporters called in to the teleconference. Dr. Volkow participated in a Satellite Media Tour which resulted in over 350 interviews, reaching close to 17 million people nationwide. Social media efforts included 21 MTF-related tweets sent from the @NIDAnews handle during and following the event, resulting in 285 retweets and 123 favorites. NIDA also used Twitter advertising, which generated 130,723 impressions, 13,959 clicks, and 133 retweets.

Facebook outreach included placing 16 MTF-related posts on NIDA's page, as well as two paid Facebook posts, generating a total of 134,931 impressions and 360 new page likes.

January 3, 2014

Severe mental illness tied to higher rates of substance use

New NIH study shows that certain protective factors do not exist in those with severe mental illness

People with severe mental illness such as schizophrenia or bipolar disorder have a higher risk for substance use, especially cigarette smoking, and protective factors usually associated with lower rates of substance use do not exist in severe mental illness, according to a new study funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

Estimates based on past studies suggest that people diagnosed with mood or anxiety disorders are about twice as likely as the general population to also suffer from a substance use disorder. Statistics from the 2012 National Survey on Drug Use and Health indicate close to 8.4 million adults in the United States have both a mental and substance use disorder. However, only 7.9 percent of people receive treatment for both conditions, and 53.7 percent receive no treatment at all, the statistics indicate.

Studies exploring the link between substance use disorders and other mental illnesses have typically not included people with severe psychotic illnesses.

"Drug use impacts many of the same brain circuits that are disrupted in severe mental disorders such as schizophrenia," said NIDA Director Dr. Nora D. Volkow. "While we cannot always prove a connection or causality, we do know that certain mental disorders are risk factors for subsequent substance use disorders, and vice versa."

In the current study, 9,142 people diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features, and 10,195 controls matched to participants according to geographic region, were selected using the Genomic Psychiatry Cohort program. Mental disorder diagnoses were confirmed using the Diagnostic Interview for Psychosis and Affective Disorder (DI-PAD), and controls were screened to verify the absence of schizophrenia or bipolar disorder in themselves or close family members. The DI-PAD was also used for all participants to determine substance use rates.

Compared to controls, people with severe mental illness were about 4 times more likely to be heavy alcohol users (four or more drinks per day); 3.5 times more likely to use marijuana regularly (21 times per year); and 4.6 times more likely to use other drugs at least 10 times in their lives. The greatest increases were seen with tobacco, with patients with severe mental illness 5.1 times more likely to be daily smokers. This is of concern because smoking is the leading cause of preventable death in the United States.

In addition, certain protective factors often associated with belonging to certain racial or ethnic groups – or being female – did not exist in participants with severe mental illness. "In the general population, women have lower substance use rates than men, and Asian-Americans have lower substance use rates than white Americans, but we do not see these differences among people with severe mental illness," said Dr. Sarah Hartz, from the Washington University School of Medicine in St. Louis and first author on the study. "We also saw that among young people with severe mental illness, the smoking rates were as high as smoking rates in middle-aged adults, despite success in lowering smoking rates for young people in the general population."

Previous research has shown that people with schizophrenia have a shorter life expectancy than the general population, and chronic cigarette smoking has been suggested as a major contributing factor to higher morbidity and mortality from malignancy as well as cardiovascular and respiratory diseases. These new findings indicate that the rates of substance use in people with severe psychosis may be underestimated, highlighting the need to improve the understanding of the association between substance use and psychotic disorders so that both conditions can be treated effectively.

For a copy of the article by Hartz et al., go to:
http://archpsyc.jamanetwork.com/article.aspx?articleid=1790914#Abstract.

For more information on the association between substance abuse and mental illness, go to http://www.drugabuse.gov/publications/comorbidity-addiction-other-mental-illnesses/why-do-drug-use-disorders-often-co-occur-other-mental-illnesses.

This study was funded by NIH, NIDA under DA062380 and DA025733; NIAAA under AA008401; NCATS under RR024992 and RR024994; NCI under CA089392; and NIMH under MH085548 and MH085542.

http://www.drugabuse.gov/news-events/news-releases/2014/01/severe-mental-illness-tied-to-higher-rates-substance-use

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January 23, 2014

New substance abuse treatment resources focus on teens

Guide on treating teen substance abuse and online education for healthcare providers now available

Resources to help parents, health care providers, and substance abuse treatment specialists treat teens struggling with drug abuse, as well as identify and interact with those who might be at risk, were released today by the National Institute on Drug Abuse (NIDA). The release came before the start of National Drug Facts Week, an annual observance to educate teens about drug abuse. NIDA is part of the National Institutes of Health.

Adolescents' drug use, as well as their treatment needs, differ from those of adults. Teens abuse different substances, experience different consequences, and are less likely to seek treatment on their own because they may not want or think they need help. Parents can work with health care professionals to find appropriate treatment, but they may be unaware that the teen is using drugs and needs help. According to the 2012 National Survey on Drug Use and Health (PDF, 3MB), only 10 percent of 12- to 17-year-olds needing substance abuse treatments receive any services.

"Because critical brain circuits are still developing during the teen years, this age group is particularly susceptible to drug abuse and addiction," said NIDA Director Dr. Nora D. Volkow. "These new resources are based on recent research that has greatly advanced our understanding of the unique treatment needs of the adolescent."

A new online publication, Principles of Adolescent Substance Use Disorder Treatment: A Research Based Guide, describes the treatment approaches. Highlights include:

- Thirteen principles to consider in treating adolescent substance use disorders
- Frequently asked questions about adolescent drug use
- Settings in which adolescent drug abuse treatment most often occurs
- Evidence-based approaches to treating adolescent substance use disorders
- The role of the family and medical professionals in identifying teen substance use and supporting treatment and recovery.

To increase early screening of adolescent substance abuse, the Substance Use Disorders in Adolescents: Screening and Engagement in Primary Care Settings educational module was created. The online curriculum resource for medical students and resident physicians provides videos demonstrating skills to use in screening adolescents at risk for or already struggling with substance use disorders. Both the patient and physician perspectives are highlighted. Although created as a training tool, the resource is also free to anyone in the public seeking information on how to interact with teens at risk for addiction. The resource was developed by the NIDA Centers of Excellence for Physician Information, in collaboration with Drexel University College of Medicine and the University of Pennsylvania School of Medicine, both in Philadelphia. NIDA has many other resources that will be promoted during National Drug Facts Week, Jan. 27-Feb. 2, 2014. For more information on this observance, go to: http://drugfactsweek.drugabuse.gov/.
http://www.drugabuse.gov/news-events/news-releases/2014/01/new-substance-abuse-treatment-resources-focus-teens

Science Spotlights and Announcements

August 12, 2013 – *Statement from NIDA Director Nora Volkow on NIDA's commitment to marijuana research*. As part of its mandate to study drug abuse and addiction, and other health effects of both legal and illegal drugs, NIDA funds a wide range of research on and related to marijuana (cannabis); its main psychoactive ingredient, THC; and chemicals related to THC (cannabinoids). This includes understanding patterns of use, its effects on the brain and behavior, and developing prevention and treatment interventions. Our scientists are also actively engaged in better understanding the cannabinoid system, where THC and other cannabinoids act in the brain and other parts of the body.
http://www.drugabuse.gov/news-events/news-releases/2013/08/statement-nida-director-nora-volkow-nidas-commitment-to-marijuana-research

August 21, 2013 – *Parents and siblings influence future drug risk in different ways.* NIH-funded research using twin and adoption studies shows that siblings exert a greater environmental influence on a person's risk for future substance use and other related disorders than was previously believed, whereas parents' influence over this risk is more genetic than environmental.
http://www.drugabuse.gov/news-events/news-releases/2013/08/parents-siblings-influence-future-drug-risk-in-different-ways

August 21, 2013 – *NIDA and Lightlake Therapeutics partner to expand access to medication to treat opioid overdose*. NIDA and Lightlake Therapeutics Inc., a biopharmaceutical company developing novel treatments for addictions and conducting clinical trials with intranasal naloxone for the treatment of binge eating disorder, have entered into a partnership to apply this technology towards the treatment of opioid overdose.
http://www.drugabuse.gov/news-events/news-releases/2013/08/nida-lightlake-therapeutics-partner-to-expand-access-to-medication-to-treat-opioid-overdose

September 20, 2013 – *NIDA updates its consumer treatment guide in recognition of National Recovery Month*. People seeking addiction treatment for themselves or loved ones now have an updated resource with questions they should ask potential treatment centers. The revised consumer guide, Seeking Drug Abuse Treatment: Know What to Ask, is evidence-based and is being released in recognition of this year's National Recovery Month.
http://www.drugabuse.gov/news-events/news-releases/2013/09/nida-updates-its-consumer-treatment-guide-in-recognition-national-recovery-month

October 23, 2013 – *No added benefit from risk-reduction counseling at HIV testing*. For persons at risk for HIV, brief risk-reduction counseling at the time of a rapid HIV test does not reduce new sexually transmitted infections in a six-month follow-up. This counseling also did not reduce rates of unprotected sex, according to a study published in JAMA.
http://www.drugabuse.gov/news-events/news-releases/2013/10/no-added-benefit-risk-reduction-counseling-hiv-testing

October 29, 2013 – *Medication to treat marijuana addiction may be on the horizon*. NIDA funded researchers report that kynurenic acid is a naturally occurring substance in the brain that can lessen the effects of THC in animal models of drug abuse and addiction. The acid acts by reducing the function of alpha-7-nicotinic acetylcholine receptors. If effective in humans, this could lead to a medication for the treatment of marijuana addiction. There are currently no approved medications for treating marijuana addiction, estimated to occur in nine percent of users.
http://www.drugabuse.gov/news-events/news-releases/2013/10/medication-to-treat-marijuana-addiction-may-be-horizon

November 1, 2013 – *Gene variant may predict whether a person will benefit from nicotine replacement therapies*. NIH-funded research showed that differences in the CYP2A6 gene -- which controls in part how fast nicotine is metabolized -- can predict whether nicotine replacement therapies (nicotine lozenge and/or nicotine patch) will be effective in helping a person quit smoking. The effectiveness of buproprion, a non-nicotine based medication often prescribed to quit smoking, was not affected by differences in this gene. This study adds to previous findings with the CHRNA5 gene, showing that screening for genetic variation may better guide personalized treatments to quit smoking.
http://www.drugabuse.gov/news-events/news-releases/2013/11/gene-variant-may-predict-whether-person-will-benefit-nicotine-replacement-therapies

November 7, 2013 – *NIDA's Dr. Wilson Compton receives Health and Human Services Meritorious Service Award.* Dr. Wilson Compton, director of NIDA's Division of Epidemiology, Services and Prevention Research, was one of ten people to receive the Health and Human Services Secretary's Award for Meritorious Service, which recognizes employees for their sustained excellence and for inspiring others to improve their performance. Awards were presented on October 31st during a ceremony that recognized 35 groups or individual employees in five award categories for their achievements in 2012. Dr. Compton was recognized for outstanding cross-agency collaborations, linking NIDA with the multiple Health and Human Services and outside agencies to reduce tobacco use and prescription drug abuse, and to improve substance abuse prevention and treatment systems.

http://www.drugabuse.gov/news-events/news-releases/2013/11/nidas-dr-wilson-compton-receives-health-human-services-meritorious-service-award

November 21, 2013 – *New breath test may detect recent marijuana use.* Marijuana causes serious impairment in motor skills, judgment, and perception, which are necessary for operating a vehicle safely. In the past, testing drivers for recent marijuana use has not been as simple as testing for alcohol, but preliminary research on the detection of THC – the main psychoactive chemical in marijuana - in the breath of marijuana smokers may change that. According to NIDA scientists who published their work in September, a new breath test they have developed can in most cases detect whether a person used marijuana within the previous ½ hour to 2.5 hours, depending on the frequency of use. This could be a valuable tool for workplace or roadside marijuana testing.
http://www.drugabuse.gov/news-events/news-releases/2013/11/new-breath-test-may-detect-recent-marijuana-use

November 22, 2013 – *New study shows that drug overdose is the leading cause of death in former prisoners.* A new study identified drug overdose as the leading cause of death in former prisoners, with prescription opioids most commonly involved in these deaths. In addition, women leaving prison had higher mortality rates from opioids, cocaine, and antidepressants than men. These findings highlight the vulnerability of former prisoners as they transition from prison to the community, suggesting the need for more effective overdose education, monitoring for medical problems, and drug treatment in prison- and community-based mental and health care systems.
http://www.drugabuse.gov/news-events/news-releases/2013/11/new-study-shows-drug-overdose-leading-cause-death-in-former-prisoners

December 12, 2013 – *Three NIH Institutes highlight collaboration for addiction research*. Today marks the website launch for the Collaborative Research on Addiction at NIH (CRAN) initiative. Comprised of representatives from the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Tobacco Control Research Branch of the National Cancer Institute (NCI), this partnership will integrate resources and expertise to advance the science and treatment of substance abuse and addiction. The new site will allow interested researchers, clinicians, and the public to follow the collaboration's initiatives. http://www.drugabuse.gov/news-events/news-releases/2013/11/three-nih-institutes-highlight-collaboration-addiction-research

December 16, 2013 – *National Institute on Drug Abuse to announce results of 2013 Monitoring the Future Survey.* NIDA held a teleconference on Wednesday, December 18, to release its 2013 Monitoring the Future (MTF) survey results. The survey, conducted earlier this year by scientists at the University of Michigan, tracks annual drug abuse trends of eighth, 10th, and 12th-grade students. NIDA is a component of the NIH.
http://www.drugabuse.gov/news-events/news-releases/2013/12/national-institute-drug-abuse-to-announce-results-2013-monitoring-future-survey

December 19, 2013 -- *Registration open for Drug Facts Chat Day; 2014 Drug IQ Challenge preview available.* Schools can now register for Drug Facts Chat Day, NIDA's annual Web chat that connects NIH scientists with teens around the country, at http://drugfactsweek.drugabuse.gov/chat/index.php. Drug Facts Chat Day occurs on Jan 28 during National Drug Facts Week, which runs from Jan 27 – Feb 2, 2014. Transcripts from last year's chat can be found at http://drugfactsweek.drugabuse.gov/chat/2013/. http://www.drugabuse.gov/news-events/news-releases/2013/12/registration-open-drug-facts-chat-day-2014-drug-iq-challenge-preview-available

December 26, 2013 -- *Research suggests new genetic target to treat cocaine addiction.* NIDA-funded research showed that a specific mutation in the CYFIP2 gene dramatically lowers responses to cocaine in a mouse model. The mutation appears to affect the CYFIP2 protein, a key player in processes underlying memory, learning, and habit formation. This research provides a new target for research into potential medications to treat cocaine addiction. http://www.drugabuse.gov/news-events/news-releases/2013/12/research-suggests-new-genetic-target-to-treat-cocaine-addiction

January 24, 2014 - *NIDA's Dr. Marilyn Huestis chosen for new National Commission on Forensic Science*
Dr. Marilyn Huestis, Chief of the Chemistry and Drug Metabolism Section in NIDA's Intramural Research Program (IRP), was selected as an *ex-officio* member of the newly-created National Commission on Forensic Science. This commission, co-chaired by the U.S. Department of Justice (DoJ) and the U.S. Department of Commerce, includes experts and researchers in forensic science as well as judges, attorneys, and law enforcement officials. The commission will help improve the practice of forensic science and develop policy recommendations for the U.S. Attorney General.
http://www.drugabuse.gov/news-events/news-releases/2014/01/nidas-dr-marilyn-huestis-chosen-new-national-commission-forensic-science

Interview Highlights: July 2013 – December 2013

Time Magazine – Dr. Nora Volkow was interviewed about Monitoring the Future.

Associated Press — Dr. Volkow was interviewed about Monitoring the Future.

NBC News – Dr. Volkow was interviewed about Monitoring the Future.

ABC Radio – Dr. Volkow was interviewed about Monitoring the Future.

USA Today – Dr. Volkow was interviewed about Monitoring the Future.

Univision – Dr. Volkow was interviewed about Monitoring the Future.

The New York Times – Dr. Volkow was interviewed about Monitoring the Future.

Diane Rehm/NPR – Dr. Volkow was interviewed about Monitoring the Future.

Wall Street Journal – Dr. Volkow was interviewed about the neurobiology of addiction.

CNBC – Dr. Volkow was interviewed about prescription drug abuse.

PBS NewsHour — Dr. Volkow was interviewed about marijuana.

Bloomberg – Dr. Wilson Compton was interviewed about Monitoring the Future.

Los Angeles Times – Dr. Compton was interviewed about Monitoring the Future.

Al Jazeera America – Dr. Compton was interviewed about Monitoring the Future.

CBS Radio – Dr. Compton was interviewed about Monitoring the Future.

PBS – Dr. Compton was interviewed about Monitoring the Future.

Reuters — Dr. Compton was interviewed about marijuana research.

Newsweek – Dr. Marilyn Huestis was interviewed about drugged driving.

Psychiatric News – Dr. Wilson Compton was interviewed about his recent appointment to Deputy Director of NIDA.

CNBC – Dr. Nora Volkow was interviewed about prescription drug abuse.

Fort Worth Weekly – Dr. Marilyn Huestis was interviewed about K2/Spice.

Our American with Lisa Ling — Drs. Volkow and Compton were interviewed about Adderall abuse and prescription drugs.

National Public Radio — Dr. Volkow was interviewed about addiction.

The New York Times — Dr. Volkow was interviewed about prescription drug abuse.

The Washington Post — Dr. Joni Rutter was interviewed about tobacco/nicotine.

Health Magazine — Dr. Susan Weiss was interviewed about prescription drug abuse among women.

USA Today — Dr. Volkow was interviewed about medical marijuana.

Univision — Dr. Volkow was interviewed about addiction.

The Nation's Health — Dr. Ruben Baler was interviewed about addiction.

Reuters News Service — Dr. Compton was interviewed about prescription drug abuse.

CBS Radio — Dr. Compton was interviewed about prescription drug abuse.

BBC Radio — Dr. Ivan Montoya was interviewed about vaccines.

USA Today — Dr. Jack Stein was interviewed about treatment.

Al Jazeera America — Dr. Steve Grant was interviewed about ecstasy.

Washington Post — Dr. Volkow was interviewed about ADHD.

Christian Science Monitor — Dr. Compton was interviewed about molly/ecstasy.

New York Times — Dr. Roy Wise was interviewed about compulsive overeating.

The Scientist — Dr. David Thomas was interviewed about opioid abuse.

Neurology Today — Drs. Compton and Michael Baumann were interviewed about K2/Spice.

Milwaukee Journal Sentinel – Dr. Kenzie Preston was interviewed about tramadol.

Newton Magazine – Dr. Nora Volkow was interviewed about addiction.

Youth Today – Dr. Ruben Baler was interviewed about synthetic marijuana.

Science News – Dr. Wilson Compton was interviewed about addiction.

WTCH AM – Dr. Baler was interviewed about drug abuse prevention.

Seattle Times – Dr. Marilyn Huestis was interviewed about marijuana drug testing.

Associated Press - Dr. Huestis was interviewed about marijuana drug testing.

Nature – Dr. Volkow was interviewed about ADHD medication.

MEETINGS/CONFERENCES

NIDA involvement at the **American Academy of Child and Adolescent Psychiatry (AACAP) Annual Meeting,** held in Orlando, Florida, October 22-27, 2013 included two symposia and a grant writing workshop. Cheryl Boyce, Ph.D. (NIDA) and Brooke S.G. Molina, Ph.D. (University of Pittsburgh School of Medicine) co-chaired a session titled "Understanding ADHD and Smoking: Current Issues and Perspectives". Presenters included Scott H. Kollins, Ph.D. (Duke University Medical Center), Alexandra Potter, Ph.D. (University of Vermont), Stephanie Cardoos, M.A. (University of California, Berkley), and Timothy Wilens, M.D. (Massachusetts General Hospital). Geetha Subramaniam, M.D. (NIDA) and Howard Moss, M.D (NIAAA) co-chaired a session titled "Medication Therapies for Youth with Alcohol and Other Substance Use

Disorders- a Hands-on Educational Experience". Kevin Gray, M.D. (University of South Carolina) participated as a presenter. NIDA staff presented a grant writing workshop titled "NIH Research Priorities & Competitive Grant Writing".

SFN/ENDURE: NIDA's Office of Diversity and Health Disparities Acting Director, Dr. Albert Avila, co-organized and presented at the NIH Blueprint initiative "**Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (ENDURE)**" pre-meeting at SFN on November 9, 2013. This initiative aims to raise interest and opportunities in neuroscience research for individuals who are typically underrepresented in the neurosciences. The goal is to provide such individuals with training at the undergraduate level, so that they are prepared to enter and successfully complete neuroscience Ph.D. programs. Dr. Avila gave a presentation on NIH research funding opportunities.

NIDA's Office of Diversity and Health Disparities Acting Director, Dr. Albert Avila, in collaboration with staff from the National Institute of Biomedical Imaging and Bioengineering organized a pre-meeting workshop on Wednesday, November 13th at the **Annual Biomedical Research Conference for Minority Students** for students from the UMBC Meyerhoff and Savannah State undergraduate STEM scholars program. The meeting provided over 40 students valuable information and advice on transitioning from undergraduate to a graduate program, graduate school admission and expectations, and small group sessions focused on addressing individual questions ranging from research proposals to funding sources.

On September 11, 2013, NIDA, in conjunction with NIAAA, NICHD, NIMH and NINDS, held **"Views By Two: Addressing Health Disparities Through Neuroscience"** with speakers, Drs. Barry Jordan (Burke Rehabilitation Hospital) and Shari Wade (Cincinnati Children's Hospital Medical Center), who presented on the topic "Fundamental Mechanisms of TBI and Implications for Health Disparities Research." The goal of the series is to increase awareness of health disparities relating to neuroscience through a collegial discussion between 2 renowned scientists on a shared topic. Flair Lindsey, Program Analyst, Special Populations Office, represents NIDA on this inter-agency planning committee.

On September 19-20, 2013, the NIDA Office of Diversity and Health Disparities hosted a two-day **NIDA Special Populations Research Development Seminar Series Workshop** in Bethesda, Maryland. Chaired by Flair Lindsey, Program Analyst, this workshop convened 15 new substance abuse investigators and NIDA-supported faculty mentors in an intensive grants development workshop setting. During the workshop, new investigators learned of NIDA's research and funding priorities and the NIH grants submission and review process, met with NIDA program staff and NIDA funded researchers, and received feedback on research proposals.

<u>NIDA's Blending Initiative-Sponsored Meetings</u>

The Society for Social Work Leadership in Health Care (SSWLHC) 2013 Annual Conference was held in Philadelphia, Pennsylvania on October 3-4, 2013. The Blending Initiative sponsored a session titled "Role of Motivational Interviewing (MI) Techniques in Social Work Practice: Treating Patients with Substance Use Disorders."

The American College of Emergency Physicians 2013 Scientific Assembly was held in Seattle, Washington on October 13-16, 2013. A pre-meeting session was co-sponsored by NIDA (the Blending Initiative) and CDC entitled "Effective Approaches to Addressing Patients with Substance Use Disorders in the Emergency Department: A Knowledge Exchange."

The American Association for the Treatment of Opioid dependence (AATOD) 2013 National Conference was held from November 10-14, 2013 in Philadelphia, Pennsylvania. On December 10, Dr. Petra Jacobs co-chaired a half-day seminar entitled: "From START to Finish: National and International Perspectives on Disseminating Treatment Outcomes for Opioid Dependence."

The Society of Teachers of Family Medicine (STFM) 2013 Conference on Practice Improvement was held November 21-24, 2013 in San Diego, California. The Blending Initiative provided support for a session entitled "Contingency Management for Substance Use Disorders: Implementation Strategies for Motivational Incentives in Family Practice."

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Dr. Jack Stein, Director, OSPC, was a panelist for the Opening Session of "A 21st Century Approach to Drug Policy" at the ONDCP Drug Policy Reform Conference on December 9, 2013, in Washington, D.C.

Dr. Jack Stein, presented a webinar "The Science Behind Prescription Drug Abuse" at the Association for Community Affiliated Plans (ACAP), Substance Abuse Collaborative Meeting on December 3, 2013.

Dr. Cathrine Sasek, Science Policy Branch, OSPC, presented "Science Careers Outside the Lab" as part of the NIDA's Early Career Investigator Workshop at the Society for Neuroscience Meeting, on November 12, 2013, in San Diego, CA.
Dr. Ruben Baler, Science Policy Branch, OSPC, presented "Disrupted Attention and Reinforcement Processes in Humans: Evidence from Brain Imaging." During a panel at the 52nd Annual ACNP Meeting, on December 8-12, 2013, in Hollywood, Fl.

Dr. Baler presented a 2 hour workshop on "The Neuroscience of Addiction" at the Gill Montague Community School Partnership, on December 4, 2013, in Western Massachusetts.
Dr. Baler presented "Disrupted Attention and Reinforcement Processes in Humans: Evidence from Brain Imaging" at the Annual Meeting of Children and Adults with ADHD (CHADD), on November 8, 2013, in Crystal City VA.

Dr. Baler presented three lectures, "Addiction and obesity: a case study in overlapping circuitry", "Sleep deprivation: the silent risk factor", and "Mental illness: an evolutionary perspective," at the III Internation Congress Dual Disorders Addictions and other Mental Disorders on October 23rd to October 26th, 2013, in Barcelona, Spain.

Dr. Samia Noursi, DCNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program co-chaired a Trans-HHS meeting, Intimate Partner Violence Screening and Counseling, on December 9, 2013. The meeting was also co-chaired by Dr. Nancy Lee, Deputy Assistant Secretary for Health -Women's Health, Director of Office on Women's Health, DHHS, and Dr. Marylouise Kelley, Director of Family Violence Prevention & Services Program, Family & Youth Services Bureau, ACF. Additional participating agencies were: the Agency of Administration for Community Living (ACL), ACF, Agency for Healthcare Research & Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration (HRSA), NIH, Substance Abuse and Mental Health Services Administration (SAMHSA), Office of the Assistant Secretary for Planning and Evaluation (ASPE), Office of Population Affairs (OPA), and the Office on Women's Health (OWH). The meeting was attended by over 150 participants, among them federal employees, researchers, practitioners and policy makers. Among the speakers was Ms. Lynn Rosenthal, the White House Advisor on Violence Against Women. Several NIDAS grantees presented their data among them md NIDA Advisory Council Member, Dr. Nabila El-Bassel. The meeting was video cast and archived at http://videocast.nih.gov.

Dr. Samia Noursi was invited to contribute to the "Trauma-Informed Approaches: Federal Activities and Initiatives, Federal Partners Committee on women and Trauma" working document. Dr. Noursi authored the NIH portion of the report http://www.nasmhpd.org/Publications/Women_and_Trauma.aspx, published in September 2013.

In collaboration with the Neuroscience consortium, Dr. Samia Noursi hosted a Cutting Edge Seminar featuring Dr. Nathalie Goletiani, Harvard Medical School on September 24, 2013. Dr. Goletiani presented on "Sex-specific Endocrine Differences as Determinants for Distinct Responses to Targeted Therapies."

Dr. Cora Lee Wetherington, DCNBR and Women and Sex/Gender Differences Research Program Coordinator, gave an invited talk, "Sex/Gender Matters in Drug Abuse," at the first annual conference, Behavior Change, Health, and Health Disparities, at the University of Vermont, September 26-27, 2013.

Dr. Cora Lee Wetherington served on the planning committee for the 10th Anniversary Interdisciplinary Women's Health Research Symposium held by the NIH Office of Research on Women's Health (ORWH) on October 24, 2013 in Masur Auditorium. The symposium featured researchers in ORWH's K12 and P50 signature programs in which NIDA participates. Dr. Wetherington moderated "Session III: Addictive Disorders and Women's Health" in which three NIDA researchers made presentations: Sherry McKee (Yale University School of Medicine), "Targeting the Noradrenergic System for Gender-Sensitive Treatment Development for Tobacco Dependence;" Erin McClure, (Medical University of South Carolina), "Varenicline Versus Nicotine Patch for Smoking Cessation Women: Efficacy Findings for a 4-Week Double-Blind Trial;" and Tomoko Udo (Yale University School of Medicine), "Sex Differences in Anticipatory Negative Contrast and Bing-Like Eating Behaviors in Mice." Posters also were presented by NIDA researchers: Elise DeVito (Yale University School of Medicine), Yann Mineur (Yale University School of Medicine), Megan Moran-Santa Maria (Medical University of South Carolina), and Marilyn Carroll (University of Minnesota).

Dr. Minda Lynch, DBNBR, lead a trans-IC planning team to organize a Science of Behavior Change (Common Fund Initiative) meeting in Sept, 2013 on "Harnessing Neuroplasticity for Behavior Change". Participants at the meeting, from animal, human, basic and clinical neuroscience research discussed the challenges of identifying and manipulating neurobiological 'targets' for behavior change, the 'value added' of neurobiological conceptual models, use of biomarkers as moderators for change, and mediational analyses to identify causative mechanisms.

Jonathan D. Pollock, Ph.D., DBNBR, spoke about areas of interest for single cell analysis research at the Single Cell Analysis Meeting at Stanford University, September 5, 2013, Palo Alto, CA.

Jonathan Pollock, Ph.D planned attendance and chairing of sessions on "Alcohol and Substance Use Disorders", October 18, 2013 and Role of Methylation and Chromatin Modification in Substance Abuse Behavior" October 18, 2013, at the World Congress on Psychiatric Genetics was cancelled due to the Government shutdown.

Dr. Da-Yu Wu, DBNBR, spoke at the Cold Spring Harbor Laboratory meeting on Rat Genomics and Models, held December 11-14, 2013 at Cold Spring Harbor, New York. His title was "Molecular, Genetic and Genomic Studies of Brain Disorder in Rat".

Dr. John Satterlee gave a presentation entitled "NIH Roadmap Epigenomics Program Overview at the "Epigenomics: A Roadmap to the Living Genome" meeting held on October 20-21 in Boston, MA.

Dr. Satterlee and Dr. Rutter, Acting Director, DBNBR, planned an exciting session entitled "Extracellular RNAs in Neuroscience: Biology, Biomarkers, and Therapeutics" for November 9, 2013, at the 2013 NIDA Frontiers in Neuroscience Miniconvention, however the miniconvention was unfortunately cancelled due to NIH Conference Approval issues.

Dr. Susan Volman, DBNBR, organized and chaired a Mini-Symposium at the Society for Neuroscience Annual meeting entitled "New Insights into the Specificity and Plasticity of Reward and Aversion Encoding in the Mesolimbic System" in San Diego, CA on November 12, 2013.

On November 1, 2013, Dr. Cheryl Anne Boyce, DCNBR, served as invited faculty for the "New Connections: Increasing Diversity of RWJF Programming Seventh Annual Research and Coaching Clinic" held in Boston, MA. The clinic was designed to assist junior and mid-career researchers from underrepresented communities with gaining skills for NIH grant writing. NIDA grantee Dr. Margarita Alegria, Harvard University, also served as faculty for this year's clinic.

Drs. Woody Lin and Steven Grant, DCNBR, have participated in a trans-NIH workgroup to plan the upcoming 10th Anniversary Meeting of the Fogerty International Center Program of Brain Research in the Developing World across the Lifespan.

Dr. Yu (Woody) Lin organized a training session entitled "Funding Opportunities for Enhancing Diversity in Addiction Research" at 2013 NIDA Exhibition Booth of the Society for Neuroscience Annual Conference in San Diego, CA, November 10-11, 2013. The activity was co-sponsored by NIDA Asian-American Pacific Islander Scholar and Researcher Workgroup and Office of Diversity and Health Disparity.

Dr. James Bjork, DCNBR, gave a talk entitled "Development of motivational neurocircuitry: The importance of individual differences" On September 21, 2013, as part of a special symposium on reward processing, held at the Inaugural FLUX Congress Conference in Pittsburgh, PA.

Drs. Steve Grant and James Bjork, DCNBR, co-chaired a symposium entitled: "Legal Damages: New Insights into Chronic Marijuana Effects on Human Brain Structure and Function" held on December 11, 2013, at the 52nd Annual Meeting of the American College of Neuropsychopharmacology in Hollywood, FL.

On November 18 and 19, 2013 Dr. Mary Kautz, DCNBR, participated in the inaugural Tobacco Centers of Regulatory Science (TCORS) 2013 Grantees Meeting, held by the NIH Tobacco Regulatory Science Program, at the Natcher Conference Center at the NIH campus in Bethesda, Maryland. This meeting allowed for grantees to learn more about working with NIH and the Food and Drug Administration (FDA) Center for Tobacco Products (CTP), collaborate with other investigators, and introduce their important work to the NIH and FDA research community.

Dr. Harold Gordon, DCNBR, presented, along with Drs. Nancy Pilottte, Roger Sorenson, and Cathrine Sasek, a workshop for new investigators at the Annual meeting of the Society for Neuroscience in San Diego, CA on November 12, 2013.

Drs. Ivan Montoya and Nora Chiang, DPMCDA, organized a two-day meeting titled Advances in the Development of Biologics to Treat Drug Addictions. The meeting was attended by more than 70 scientists, including 20 speakers. The purpose of the meeting was to review the current development of biologics to treat addictions, identify scientific gaps, opportunities and directions, and to promote collaboration among scientists in this field. The meeting took place at the Neuroscience Center on September 12 and 13, 2013.

Dr. Kevin Walton, DPMCDA, organized a trans-NIH Workshop on Electronic Cigarettes, supported by NIDA and 6 other ICs, to discuss the highest priority issues on these devices and to identify where NIDA and NIH can have the most impact in evaluating the effect of electronic cigarettes on nicotine addiction and the public health. The one day workshop invited 12 external speakers to cover topics that included the engineering of the devices, addiction potential, biomarkers, adolescent use, dual use with tobacco, and effective design of nicotine and tobacco cessation clinical studies. Additional presentations from the FDA CTP and CDER explored the current and possible future regulatory landscape. Interest in the workshop was very high and observers included representatives from the World Health Organization, Health Canada, and the presidents of both the Society for Research on Nicotine and Tobacco and the College on Problems of Drug Dependence. Deliverables from the workshop include support from the

attendees for evaluating the creation of a standardized electronic cigarette for use in clinical studies, further trans-NIH coordination of research on electronic cigarettes, and possible publication of the proceedings in a special issue of Nicotine & Tobacco Research focusing on electronic cigarettes.

Dr. Jag Khalsa, DPMCDA, presented at the ASAM State-of-the-Art Biennial Medical Scientific Conferencev on *Marijuana Changing Laws: Where do we go from here?* Drs. Robert DuPont, Corey Waller and John Klopf presented on the social and economic, and medical/health consequences of possibly increased use of legalized marijuana, and policy issues related to the changing laws on marijuana, October 22-24, 2013, Crystal City, Virginia.

Dr. Jag Khalsa presented a symposium on Drug Abuse and HIV and Aging at the Annual Meeting of HIV Aging, in Baltimore, October 30-31, 2013. Drs. Greg Lucas of Johns Hopkins and Dr. Steven Woods of UCSD presented their current research on impact of drug abuse in HIV-infected older populations.

Dr. Redonna K. Chandler, DESPR co-chaired a panel entitled, Alcohol and other Drug Screening and Brief Intervention: Questions about Efficacy and Implementation at the 2013 Addiction Health Services Research Meeting, Portland, OR, October 24, 2013.

Dr. Redonna K. Chandler chaired a panel entitled, Research on Substance Use Disorder Treatment and Associated HIV Services in this Time of Rapid Change: What's Being Done? At the 2013 Addiction Health Services Research Meeting, Portland, OR, October 25, 2013.

Dr. Redonna K. Chandler presented a plenary entitled, The Treatment of Substance Use Disorders in Criminal Justice Settings at the Center for Health & Justice Public and Police Safety Task Force Meeting, Chicago, IL, November 19, 2013.

On November 7, 2013, Dr. Harold Perl, DESPR presented "The DRAMA Model: MI Skills to Engage Patients and Initiate the Discussion of Substance Abuse in Internal Medicine" Presented at annual conference of AMERSA in Bethesda, MD.

On September 19-20, 2013, Dr. Dionne Jones, DESPR, participated in the Research Development Seminar Series Workshop sponsored by NIDA's Office of Diversity and Health Disparities, mentoring junior investigators in preparing grant applications for submission to NIDA.

On October 23-25, 2013, Dr. Dionne Jones participated in a session on 'Group Mentoring for Early Career Investigators' at the Addiction Health Services Research Conference, Portland, OR,

On November 2-6, 2013, Dr. Dionne Jones chaired a panel on 'Alcohol, Sexual Risk and HIV: New Findings on Women and Men' at the American Public Health Association Annual Meeting held in Boston, MA.

Dr. Eve Reider, DESPR, represented NIDA in participating in the development of a National Research Action Plan (NRAP) in collaboration with the DoD, VA, Department of Education, and other NIH institutes (NIMH, NIAAA).

In October 2013, Dr. Richard Jenkins, DESPR, participated in the CFAR mentoring program at the Centers for AIDS Research (CFAR) Social and Behavioral Science Research Network meeting at George Washington University in Washington DC.

On October 28-29, 2013, Dr. Augusto Diana, DESPR, organized and chaired a session titled, "Planning for Phase III," at the SBIR/STTR Annual Conference in Sioux Falls, South Dakota.

On September 17-18, 2013, Dr. Eve Reider, DESPR, participated in a forum on "Military Families in Transition: Stress, Resilience, and Well-Being." The forum was sponsored by the Department of Psychiatry and Center for the Study of Traumatic Stress at the Uniformed Services University of the Health Sciences held at the Walter Reed Army Institute of Research in Silver Spring, Maryland.

On October 15, 2013, Dr. Eve Reider attended the open session of the Institute of Medicine and National Research Council of the National Academies Board on Children, Youth and Families' Fall 2013 Board Meeting, which was held at the National Academies, Keck Center, in Washington, D.C.

On December 19, 2013, Members of the Prevention Research Branch (PRB), NIDA, met with Mike Zeliff, Ph.D., Marine Corps, to hear an update on the prevention activities he has completed with the Marine Corp during the past year. The meeting was held at NIDA.

On Thursday, September 19, 2013, Dr. Aria Crump, DESPR, presented a talk on DESPR Program Priorities and Interest Areas at the NIDA Special Populations Research Development Seminar Series Workshop.

In October 2013, Dr. Richard Jenkins, DESPR, presented on implementation practice at the American Evaluation Association meeting in Washington DC, and also served as a discussant for panel on implementation evaluation at that same meeting.

In October 2013, Dr. Lori Ducharme, DESPR, delivered a plenary address on "Innovation, Integration and Implementation" at the 2013 Addiction Health Services Research conference, Portland OR.

In November 2013, Dr. Lori Ducharme co-presented a panel on "Expanding Access to Medication Assisted Treatment for Offenders at Re-Entry" at the 2013 meetings of the American Association for the Treatment of Opioid Dependence (AATOD), Philadelphia PA.

Dr. David Liu, CCTN, chaired a workshop entitled "Medication-Assisted Treatments for Substance Use Disorders" at the 37th Annual National Conference of the Association for Medical Education and Research in Substance Abuse (AMERSA) held November 7-9, 2013 in Bethesda, Maryland. The workshop received the 2012 conference's Best Workshop Award.

Dr. Anto Bonci Director, IRP, was an instructor at the Cold Spring Harbor Cellular Biology of Addiction Course and Chair of the 2013 Gordon Research Conference on Catecholamine in West Dover, VT in August 2013.

Dr. Bonci had been invited to speak at the Flexner Lecturer at The University of Pennsylvania and at the 3rd World Parkinson Congress and be keynote speaker at the First Joint Meeting of the Latin American Researcher Network on Drug Addiction (LARNEDA) and the Latin American Society of Biomedical Research on Alcoholism (LASBRA) in October. However, all October speaker engagements were cancelled to due to the furlough.

Dr. Amy Newman, IRP, gave invited lectures at the 2013 Gordon Research Conference on Catecholamines, and the Department of Medicinal Chemistry, Purdue University in August and at the NIAAA-Intramural Research Program in December.

Dr. Jean Lud Cadet, IRP, attended the Society for Neuroscience meeting held in San Diego, California where he presented "Genome-wide analysis of histone H4K5 acetylation reveals a role for H4K5Ac binding as a regulator of a subset of methamphetamine-regulated genes in the rat striatum" on November 10, 2013.

Dr. Irina Krasnova, IRP, attended the Society for Neuroscience meeting held in San Diego, California where she presented "DNA Methylation in a Rat Model of Methamphetamine Addiction" on November 10, 2013.

Dr. Subramaniam Jayanthi, IRP, submitted a poster to the Society for Neuroscience meeting held in San Diego, California entitled "Delayed effects of methamphetamine on neuropeptide expression in the rat nucleus accumbens."

Dr. Mike McCoy, IRP, submitted a poster to the Society for Neuroscience meeting held in San Diego, California entitled "Transcriptional effects of a two-injection model of methamphetamine addiction on immediate early gene expression."

Dr. Stephen Heishman, IRP, attended the BEST Research Symposium on September 28 at the Inner Harbor's Columbus Center where the 15 teachers in the 2013 BEST Project presented posters on their summer projects.

Dr. Oluyomi Okunola-Bakare, IRP, co-chaired the NIH Baltimore Fellows Symposium in November and she and Dr. Thomas Keck gave invited lectures as 2014 FARE award winners.

Drs. Marta Concheiro and Ariane Wohlfarth, IRP, gave invited lectures in September at the conference "Applications of Higher Resolution Mass Spectrometry in Drug Testing" organized by the New York State Division of Criminal Justice Services. The lecture was webcasted and is now permanently available online at RTI International. Dr. Concheiro gave an invited lecture "Liquid chromatography high resolution mass spectrometry (Q exactive) confirmation methods," and Dr. Wohlfarth also gave an invited lecture on "High resolution accurate mass spectrometric methods for toxicology" at the Society of Forensic Toxicology in Orlando, Florida in October 2013.

Dr. Marilyn Huestis, IRP, and Dr. Steve Gust, Director, NIDA International Program, co-chaired a NIDA-sponsored session on "Designer drugs: The new face of drug abuse" at the International Council on Alcohol, Drugs, and Traffic Safety (ICADTS) in Brisbane, Australia.. Dr. Huestis also was appointed Chair of the Illicit Drugs and Driving Workgroup and met with researchers, academics and professionals from around the world to discuss and present the latest research being undertaken in the field.

Dr. Marilyn Huestis was on the organizing committee of the 13th International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and was chair of the plenary speaker committee in Salt Lake City, UT.

Dr. Marilyn Huestis was selected as the 2013-2014 Meyer Bodansky Visiting Professor of Experimental Pathology at the University of Texas Medical Branch (UTMB) in Galveston, Texas. Dr. Huestis presented pathology grand rounds on the effects of chronic cannabis exposure and a public lecture on designer drugs.

Dr. Elliott Stein, IRP, was an invited speaker at the NIH Tobacco and Nicotine Research Interest Group in Bethesda, MD in July 2013; his talk was entitled “Multimodal neuroimaging genetic biomarkers of nicotine addiction.” He also delivered an invited talk at the Research Institute on Addictions, University of Buffalo in November 2013 entitled “Imaging genetic biomarkers of nicotine addiction.”

Dr. Roy Wise, IRP, gave the History of Neuroscience Lecture at the annual meeting of the Society for Neuroscience.

Dr. Yavin Shaham, IRP, gave invited lectures at Washington State University, Oregon Health Science University, Washington University, Johns Hopkins University, Wake Forest University, and INSERM, Bordeaux, France. He also served as a committee member on a Society for Neuroscience award committee (Jacob P. Waletzky Award) and gave an invited lecture at the EBPS meeting in La Rochelle, France.

Dr. George Uhl, IRP, presented invited talks at Boston University and Johns Hopkins University Schools of Medicine. He assumed co-chair of the NIH Translational Research Interest Group, completed service on the NIAAA 01 study section, and provided reviews for CSR, NIDA, and NIAAA review panels, and for the Restless Leg Syndrome foundation. Addiction Reviews, which Dr. Uhl founded and edits, achieved an > 13 impact factor.

PLANNED MEETINGS **** (Pending approval)***

2014 Community Anti-Drug Coalitions of America (CADCA) National Forum– National Harbor, MD, February 3-6, 2014.*
NIDA staff will deliver two sessions at the CADCA National Forum. Ruben Baler, Ph.D. (NIDA) will present "Where do Addictions Come from?" and Jacqueline Lloyd, Ph.D., (NIDA) will chair a session on "Cultural and Contextual Adaptation of Evidence-Based Prevention Interventions for Real World Community and Practice Settings." The session will highlight the ongoing research being conducted by Dr. Jeanne Poduska (American Institutes for Research, Baltimore, MD) on the Good Behavior Game, which is an evidence-based classroom behavior management strategy. Dr. Volkow will deliver the plenary address, and there will be a Power Session delivered by Drs. Wilson Compton and Jack Stein titled *Science Update from NIDA: Spotlight on Marijuana-Related Research*

2014 American Psychiatric Association Annual (APA) Meeting – New York, NY, May 3-7, 2014.*
NIDA will hold a track of sessions at the APA Annual Meeting. Dr. Nora Volkow is scheduled to deliver the Frontiers of Science Lecture, and hold an interactive session with residents. NIDA staff will chair sessions on a variety of substance abuse related topics including: Cannabis Use and Youth: Risk Assessment and Implications for Clinical Practice, The Role of Substance Use in Violence Against Self and Others, Persistence and Desistance of Comorbid Drug Abuse and Psychiatric Disorders in Adolescence, Biological Approaches To Treat Substance Use Disorders, and Diagnostic and Assessment Considerations for the Treatment of Comorbid Opioid Addiction and Chronic Pain.

College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting – San Juan, Puerto Rico, June 14–19, 2014.*
The National Institute on Drug Abuse (NIDA) will sponsor a Grant-Writing and Career Development Workshop at the CPDD Annual Scientific Meeting. The Grant/Career Workshop provides new or junior investigators with information and skills to advance their research careers, with a heavy emphasis on NIDA funding opportunities, grantsmanship, and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference. Only NIDA-supported NRSA trainees, NRSA fellows, and Minority Supplement recipients are eligible for this award. The application deadline for these awards was December 19, 2013.

The NIDA CTN Steering Committee Meeting will be held March 11-13, 2014 in Gaithersburg, MD.

STAFF HIGHLIGHTS

Staff Honors and Awards

Donna Calu, Ph.D., IRP, received the 2014 Winter Conference in Brain Research Travel Fellowship and is an invited lecturer at the 47th Winter Conference in Brain Research in Steamboat Springs, Colorado.

Chien-Ying Chuang, **Ph.D.**, IRP, was the recipient of an NIH FARE award.

Lori Ducharme, Ph.D., DESPR, Services Research Branch, was appointed to the Executive Committee of the Veteran's Administration's Substance Use Disorder Quality Enhancement Research Initiative (QUERI).

Marilyn Huestis, Ph.D., IRP, was reappointed to the World Anti-doping Agency Prohibited Drug List Committee that determines the list of prohibited substances for all elite sports.

Anton Ilango Micheal, Ph.D., IRP, received the 2014 NIDA-IRP postdoctoral FARE award.

Mary Pfeiffer, Ph.D., Assistant Director, Office of Education and Career Development, IRP, received the NIH Director's Award for her work on the Feds Feed Families project.

Tsung-Ping Su, Ph.D., IRP, was appointed by the Johns Hopkins University in October as a member of the Johns Hopkins Graduate Board of Examiners in October 2013.

Dong Wang, Ph.D., IRP, received the 2014 NIDA-IRP postdoctoral FARE award.

Staff Changes

New Employees

Sandrine Pirard Janne d'Othee, M.D., Ph.D., M.P.H. joined the Chemistry and Drug Metabolism Section, IRP, as staff clinician in August 2013.

Heather Kimmel, Ph.D., joins the Epidemiology Research Branch in DESPR. Dr. Kimmel received her undergraduate degree in biology from Wake Forest University and her Ph.D. in neuroscience from Emory University. As a faculty member at Emory University, she examined the effects of psychostimulants on neuropharmacology and behavior in rodent and nonhuman primate models of addiction, and was also involved in medication development efforts to help treat those addicted to psychostimulants. She comes to us more recently from an AAAS Science & Technology Policy fellowship in the Economics, Exposure, and Technology Division at US EPA. Heather will be developing the tobacco program in DESPR, including activities relating to the PATH study and other collaborations with the Center for Tobacco Products at FDA.

Avni Shah, M.D., M.P.H. joins DESPR and the PATH Study. Dr. Shah comes to us most recently from Georgetown University, where she worked on several clinical trials. By way of training, Avni is a medical doctor, holds an MPH in Environmental Health Sciences, and earned a graduate certificate in biostatistics (while she was working at Georgetown). Avni joins the PATH Study to increasingly assume responsibilities in the areas of data management and data analysis (both topics are becoming increasingly demanding and important for PATH), and to contribute substantively to the long-term plans for bio specimens. She also has experience with tobacco-cessation interventions, and will likely contribute to plans/papers/analyses on topics related to cessation.

Eric Wargo, Ph.D. joined the Science Policy Branch, Office of Science Policy and Communications (OSPC) in December 2013 as a Health Science Policy Analyst. Dr. Wargo received his Ph.D. in Anthropology from Emory University in 2000 and has since worked as a writer and editor in Washington, D.C. From 2005 through 2011, he was Editorial Director at the Association for Psychological Science (APS) and Managing Editor of the APS journals *Current Directions in Psychological Science* and *Psychological Science in the Public Interest*. He joined the Science Policy Branch of OSPC as a science writer contractor in January 2012.

Rachel Wolf joined the Office of Science Policy and Communications' Public Information and Liaison Branch in November 2013 as the NIDA Deputy Press Officer. Before joining NIDA, Rachel was a CDC contractor working for the Oak Ridge Institute for Science and Education and on other CDC contracts as well as working with the CDC communications office. Rachel has a Bachelor's in Biology and a Masters in Behavioral Sciences and Health Education.

New Appointments/Transfers

Wilson Compton M.D., M.P.E. of the Division of Epidemiology, Prevention, Research and Services Branch (DESPR), is appointed as the Deputy Director for the National Institute on Drug Abuse (NIDA). Dr. Wilson Compton is a well-recognized expert in the addiction field with over two decades of research, clinical, and administrative experience. For the past 10 years, he has been the Director of the Division of Epidemiology, Services and Prevention Research (DESPR) at NIDA where he very competently and creatively managed a large and complex research program of national and international scope spanning a broad range of population-based science. Prior to joining NIDA, Dr. Compton was Associate Professor of Psychiatry and Director of the Master in Psychiatric Epidemiology Program at Washington University in Saint Louis as well as Medical Director of Addiction Services at the Barnes-Jewish Hospital in Saint Louis. He received his undergraduate education from Amherst College and attended Washington University School of Medicine where he also completed his residency training in psychiatry and later graduated from the Master in Psychiatric Epidemiology program. In 2008, he received the Senior Scholar Health Services Research Award from the American Psychiatric Association and in 2010 the Paul Hoch Award from the American Psychopathological Association. Dr. Compton is highly respected as a scientist and has been a prolific author of over 100 articles, book chapters, research manuals, and invited publications.

Redonna Chandler, Ph.D. assumed the position of Acting Director for the Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse, Bethesda, MD. Dr. Chandler is an expert in the treatment of substance use disorders with experience in research, clinical practice, and science administration. For the past 12 years she has served in numerous positions at NIDA including 7 years as the Chief of the Services Research Branch where she managed a portfolio of research intended to improve the quality of treatment services effectively addressing substance use disorders and HIV. Prior to joining NIDA, Dr. Chandler worked for the Bureau of Prisons implementing and evaluating substance abuse treatment programs for federally sentenced offenders and served as an adjunct professor at the University of Kentucky. Dr. Chandler earned her Ph.D. in psychology from the University of Kentucky and has authored numerous peer-reviewed articles and book chapters. Dr. Chandler has been recognized with several awards for her scholarship and leadership in drug abuse research.

Lori Ducharme, Ph.D. is serving as Acting Deputy Branch Chief, Division of Services Research Branch, DESPR.

David Daubert has been appointed NIDA's Deputy Executive Officer. Dave has provided administrative leadership at NIDA for the past eleven years, serving first as Deputy Chief of OM's Administrative Management Branch (AMB) and then Chief, AMB since 2005. Prior to joining NIDA, he served as a Budget Analyst at NIMH's Intramural Research Program and an Administrative Officer at NIMH's Extramural Program. Dave has been a leader on several NIH-level groups and initiatives including the Extramural Administrative Management Council and the NIH Administrative Strategic Plan. Dave holds a degree in Management Technology and has received numerous performance awards including the NIH Director's Award.

Nathaniel Fredericks is serving as Acting Chief of OM's Administrative Management Branch for a 90-day period effective January 1, 2014.

Sheri Grabus, Ph.D. was appointed as the NIDA Press Officer in December 2013. Dr. Grabus previously served as the Acting NIDA Press Officer for the past year and before that served as the NIDA Deputy Press Officer for 3 years.

Dionne Jones, Ph.D. is serving as Acting Branch Chief, Division of Services Research Branch, DESPR.

Departures

Helio Chaves, NIDA's Deputy Executive Officer, has accepted a new position as Deputy Executive Officer at the FDA, Center for Food Safety and Applied Nutrition (CFSAN), Office of Management. In his new role, Helio will support the CFSAN's mission of ensuring the nation's food supply is safe, by supporting and overseeing Business Informatics, Administrative Services, Acquisition Management, Budget, Workforce Management and Facilities. Helio has been with NIDA since March of 2012 and has played a key role in the oversight of the Office of Management's myriad operations, the transformation of several business processes, and has also served as Acting IRMB and AMB Chief.

Gaya Dowling, Ph.D. left NIDA after 10 years in the Science Policy Branch, OSPC in December. As Chief of the Science Policy branch, Gaya's contributions to NIDA have been enormous. Her scientific and policy expertise have helped shape a host of critically important projects ensuring information was scientifically accurate, well written, and reflective of the latest research. Dr. Dowling is currently serving as the Acting Director of the Office of Science and Technology with the National Heart, Lung, and Blood Institute (NHLBI) where she will be leading the coordination and assessment of progress on cardiovascular, lung, and blood diseases.

Denise Pintello, Ph.D., OD, left NIDA in December 2013 to become the Program Chief of the NIMH Child and Adolescent Services Research portfolio. Denny began her 11-year career at NIDA in OSPC, where she oversaw NIDA's Blending Research and Practice Initiative.
In 2005 she was selected to serve as the Special Assistant to NIDA's Deputy Director, where she worked closely with national leaders from NIDA's National Advisory Council on Drug Abuse to coordinate Council review workgroups and prepared ten final reports including: NIDA's Blue Ribbon Task Force on Health Services Research, the National Drug Abuse Treatment Clinical Trials Network, NIDA's Medications Development Program, NIDA's Science of Genetics Review and most recently, the Blue Ribbon Task Force on NIDA's Intramural Research Program. While at NIDA, Denny was selected to receive multiple awards including the NIDA Director's Award for the Roadmap Behavioral and Social Sciences Initiative, the Blending Intramural and Extramural Collaboration and in 2013, the NIH Director's Award for the NIH Pain Consortium's Centers of Excellence in Pain Education.

Petra Jacobs, M.D., Acting Deputy Director for CCTN, left NIDA in November 2013 to join her husband and family in Ecuador. Geetha Subramaniam, MD, FAPA, who previously served as Team Leader and Medical Officer in the CCTN, was appointed the Deputy Director, CCTN, NIDA in September 2013.

Scott Chen, Ph.D., SRO, OEA, transitioned to a position with NCI on December 28, 2013.

Chien-Ying Chuang, Ph.D., IRP, was appointed an Assistant Professor of Neuroscience at the Biomedical Institute of the Taipei Medical University, Taipei, Taiwan, in August, 2013.

Teruo Hayashi, Ph.D., IRP, was appointed as the Executive Director of the Nishikawa Hospital in Shimane prefecture, Japan.

Retirements

Jerry Frankenheim, Ph.D., DBNBR, is retiring after 25 years at NIDA. Jerry was trained as a pharmacologist and earned his PhD at the University of Mississippi Medical Center He has been a member of DBNBR's neuroscience branch under Roger Brown and Nancy Pilotte. During his time at NIDA, Jerry's interests have focused on the neural mechanisms of drug abuse, circuitry, neuroplasticity and neurotoxicity. He has developed a wide-ranging portfolio in emergent drugs of abuse including the hallucinogens, GHB and MDMA. Jerry has been an active member of the Neuroscience Consortium and has worked with the Office of Special Populations to support the minority supplement program. Jerry has many interests, and when he is not skiing or cycling his

way through retirement, he will volunteer his time to help us to think about how drug abuse accelerates aging.

Amrat Patel, Ph.D., Director of the Pharmacokinetics Program, DPMCDA, retired on January 11, 2014 after 23 years of federal service. Prior to joining DPMCDA in 1998, Dr. Patel had 10 years of research experience in receptor pharmacology and drug abuse research at the University of Virginia and the NIDA IRP, as well as 2 years of FDA experience in bioequivalence/ pharmacokinetics. He brought to DPMCDA a broad knowledge of both basic research and regulatory science. During his first 5 years at DPMCDA, he served as a pharmacologist for the Addiction Treatment Discovery Program, where he was responsible for the identification of new compounds for the treatment of drug abuse. In 2003, he assumed the responsibility for directing the pharmacokinetic and metabolism projects pertaining to medications development. He was a member of various medication development project teams and NIDA workgroups including the Genetics Work Group and the Special Populations Review group. He made significant contributions to NIDA's medications discovery and development program

Jane Smither retired from the Science Policy Branch, OSPC in September 2013, with 34 years of government service, 17 with NIDA. Ms. Smither joined OSPC in October 1996 as a Program Analyst. While she played a key role in all aspects of NIDA public outreach activities, her primary role was that of NIDA Constituent Relations Liaison, which encompassed a wide range of activities, special projects, and collaborations with key outside organizations to advance NIDA's mission. Prior to NIDA, Ms. Smither served as a senior staff member to Congressman E. (Kika) de la Garza of South Texas for 16 years.

GRANTEE HONORS

Carolyn Mazure, Ph.D., Director of Women's Health at Yale, was named to a new endowed professorship that provides permanent leadership for Women's Health Research at Yale, the University's interdisciplinary research center focused on women's health and gender differences. Dr. Mazure, who founded Women's Health Research at Yale in 1998 and has been Director from the start, is the inaugural Norma Weinberg Spungen and Joan Lebson Bildner Professor of Women's Health Research at Yale.

David Olds, Ph.D., Professor of pediatrics, nursing, psychiatry and public health at the University of Colorado School of Medicine and founder of the Nurse –Family Partnership (NFP) program is the 2012-2013 recipient of the Chase Faculty Community Service Award. Each year a faculty member at the University of Colorado who provided exceptional service to the community is honored. Dr. Olds is recognized for the extraordinary impact and benefits of his work to children and families worldwide.

CTN New England Consortium Node

John Hamilton, LMFT, CEO of Recovery Network of Programs, Inc. (Connecticut) was one of 8 recipients of the 2013 *Nyswander/Dole "Marie" Award*. Awardees are nominated and selected by their peers for outstanding service in the opioid treatment community. The awards were presented at the 2013 American Association for the Treatment of Opioid Dependence, Inc. (AATOD) Conference in Philadelphia on November 12, 2013. Dr. Vincent Dole and Dr. Marie Nyswander were the first recipients of this Award in 1983. The Association has been responsible for bestowing this honor since the first Regional Conference of 1984 in New York.

Shelly F. Greenfield, M.D., M.P.H. from the New England Consortium Node was recently awarded the R. Brinkley Smithers Distinguished Scientist Award from the American Society of Addiction Medicine (ASAM) for 2014. The award was established by ASAM in 1995 and is presented annually. Dr. Greenfield has been invited to receive the award and deliver the keynote plenary address at the society's annual medical scientific conference on April 11, 2014, in Orlando, Florida. The 45th Annual Medical-Scientific ASAM Conference is scheduled for April 10-13, 2014.

CTN Southern Consortium Node

Kathleen T. Brady, M.D., Ph.D., Distinguished University Professor and Principal Investigator of the Southern Consortium Node, received the 2013 Medical University of South Carolina's (MUSC) Women Scholars Faculty Advancement Award. This award recognizes the MUSC faculty member who best demonstrates excellence in his/her commitment to the advancement of women faculty. In recognizing Dr. Brady, the Women Scholars Initiative Committee welcomed the opportunity to publicly recognize her and thank her for the vision and opportunities she provides to women faculty.

MacArthur Foundation Award

Susan Murphy, Ph.D., received the prestigious John D. and Catherine T. MacArthur Foundation Award. Dr. Murphy is a statistician who is developing new methodologies to evaluate courses of treatment for individuals coping with chronic or relapsing disorders such as depression or substance abuse. Her work has influenced many in the CTN.

AMERSA Awardees from the CTN

The Association for Medical Education and Research in Substance Abuse (AMERSA) held its 37th National Conference in Bethesda, Maryland, November 7-9, 2013. The conference brought together researchers and health professional educators to learn about scientific advances and teaching approaches. Several CTN members were recognized at this meeting:

- **George Woody, M.D.** received the John P. McGovern Award.
- **David Liu, M.D.**, **Marc Fishman, M.D.**, and **Ned Nunes, M.D.** received the Best Workshop Award.
- **Jennifer McNeely, M.D.** received the John Nelson Chappel Research Award.
- **Joshua Lee, M.D.** received Best Research Abstract Semi-finalist Award.